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(54) Title: COMPOUNDS FOR INHIBITING COPPER-CONTAINING AMINE OXIDASES AND USES THEREOF

(57) Abstract: This invention is directed to inhibitors of copper-containing amine oxidases (E.C.1.4.3.6) including semicarbazide-sensitive amine oxidase (SSAO; also known as vascular adhesion protein- 1, VAP-I), and their therapeutic use in inflammatory diseases, diabetes and its associated complications, atherosclerosis, neurodegenerative diseases, obesity, hypertension and cancer.

COMPOUNDS FOR INHIBITING COPPER-CONTAINING AMINE OXIDASES AND USES THEREOF

This applications claims priority to U.S. provisional application Serial No. 60/598,010, filed August 2, 2004, the disclosure of which is explicitly incorporated by reference herein.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to inhibitors of copper-containing amine oxidases (E.C. 1.4.3.6). Specifically, the invention provides inhibitors of semicarbazide-sensitive amine oxidase (SSAO; also known as Vascular adhesion protein-1 VAP-1). The invention provides methods for using such compounds as therapeutic agents for treating inflammatory diseases, diabetes and its associated complications, atherosclerosis, neurodegenerative diseases, obesity, hypertension and cancer.

2. Background of the Related Art

Semicarbazide-sensitive amine oxidase (SSAO)/ Vascular Adhesion Protein-1 (VAP-1) is a bifunctional membrane protein. One function of this protein is as a copper-containing ectoenzyme with amine oxidase activity that can be inhibited by carbonyl-reactive compounds such as semicarbazide (Lyles, 1996, *Int. J Biochem. Cell Biol.* 28:259-274). SSAO oxidizes a primary amine into the corresponding aldehyde with production of hydrogen peroxide and ammonia according to the following reaction:

$$R\text{-}CH_2\text{-}NH_2 + O_2 \rightarrow R\text{-}CHO + H_2O_2 + NH_3$$

SSAO/VAP-1 is also an adhesion molecule implicated in inflammation processes (Bono *et al.*, 1999, *Amer J Pathol* 155:1613-1624; Salmi & Jalkanen, 1992, *Science* 257:1407-1409; Smith *et al.*, 1998, *J Exp. Med.* 188:17-27)

SSAO/VAP-1 is expressed in a variety of tissues, including endothelial cells, lung, smooth muscle cells, and (under normal conditions, highly expressed) in adipose tissue cells. SSAO/VAP-1 is not expressed in 3T3-L1 fibroblasts, but is induced during adipogenesis (Fontana *et al.*, 2001, *Biochem. J* 356:769-777; Moldes *et al.*, 1999, *J Biol. Chem.* 274:9515-9523).. This suggests that SSAO/VAP-1 is a member of the adipogenic gene program and, in

addition, that SSAO/VAP-1 may contribute to the acquisition of some final characteristics of fully differentiated adipose cells.

SSAO substrates are known to strongly stimulate glucose transport and recruitment of GLUT4 to the cell surface in isolated rat adipocytes or 3T3-L1 adipocytes (Enrique-Tarancon *et al.*, 1998, *J Biol. Chem.* 273:8025-8032; Enrique-Tarancon *et al.*, 2000, *Biochem. J* 350:171-180; Fontana *et al.*, 2001, *Biochem. J* 356:769-777; Marti *et al.*, 1998, *J Pharmacol. Exp. Ther.* 285:342-349).. Stimulation of glucose transport by SSAO substrates has also been demonstrated in isolated human adipocytes (Morin *et al.*, 2001, *J Pharmacol. Exp. Ther.* 297:563-572).

The identity of SSAO and VAP-1 has more recently been established (Bono *et al.*, 1999, *Amer J Pathol* 155:1613-1624; Smith *et al.*, 1998, *J Exp.Med.* 188:17-27) VAP-1, first disclosed in Salmi *et al.* in 1992 (Salmi & Jalkanen, 1992, *Science* 257:1407-1409) is upregulated (*i.e.*, its expression increases) on the vascular endothelium at inflammation sites, and mediates a multistep adhesive process leading to the transmigration of leukocytes from the circulation into inflamed tissues. Lymphocyte adhesion to endothelial cells is mediated by SSAO/VAP-1 in a sialic acid-dependent manner (Bono *et al.*, 1998, *J Immunol.* 160:5563-5571) and more recently it has been shown that the SSAO amine oxidase activity of VAP-1/SSAO also participates to the adhesive function of VAP-1 (Salmi *et al.*, 2001, *Immunity.* 14:265-276)..

VAP-1/SSAO has been implicated in a variety of inflammatory responses through its enzymatic activity. These include lymphocyte adhesion (Kurkijarvi *et al.*, 1998, *J Immunol.* 161:1549-1557; Salmi & Jalkanen, 1992, *Science* 257:1407-1409; Salmi *et al.*, 2001, *Immunity.* 14:265-276); and production of aldehydes like formaldehyde or methylglyoxal, putatively endogenous products of SSAO, by generating protein cross-linking and advanced glycosylation end-product (AGE) formation (Yu, 1998, *J Neural Transom. Supply* 52:201-21). Additionally, VAP-1/SSAO has the capacity to promote LDL oxidation *in vitro* (Exner *et al.*, 2001, *Cardiovasc. Res.* 50:583-588) (perhaps through its copper ion), and mice overexpressing VAP-1/SSAO in endothelial cells have a propensity to atherosclerosis (Stolen *et al.*, 2004, *FASEB* J. 18: 702-704).

VAP-1/SSAO has also been implicated in cardiovascular complications associated with diabetes, adipogenicity, apoptosis secondary to stroke and hypertension. The higher activity of SSAO associated with diabetes as well as a higher concentration of its putative endogenous substrates, methylamine and aminoacetone, may result in greater production of formaldehyde, methylglyoxal and hydrogen peroxide in diabetics than in normal individuals.

These products are highly cytotoxic for endothelial cells, which may lead to cardiovascular complications associated to diabetes (Yu, 1998, *J Neural Transm. Suppl* 52:201-218).

In addition to membrane-bound adhesion molecules, soluble isoforms of SSAO/VAP-1 have been detected in blood plasma from healthy individuals (Gearing & Newman, 1993, *Immunol. Today* 14:506-512, 1993; Kurkijarvi *et al.*, 1998, *J Immunol.* 161:1549-1557; Rothlein *et al.*, 1991, *J Immunol.* 147:3788-3793). The soluble form of VAP-1/SSAO is found in healthy adult plasma at concentrations of 50-140 ng/mL, which is enhanced in inflammatory liver diseases (Kurkijarvi *et al.*, 1998, *J Immunol.* 161:1549-1557), cardiovascular pathologies (Boomsma *et al.*, 1997, *Cardiovasc. Res.* 33:387-391), endstage of renal disease (Kurkijarvi *et al.*, 2001, *Eur. J Immunol.* 31:2876-2884), obesity (Meszaros *et al.*, 1999, *Metabolism* 48:113-117; Weiss *et al.*, 2003, *Metabolism* 52:688-692) type I diabetes (Hayes & Clarke, 1990, *Res. Commun. Chem. Pathol Pharmacol.* 69:71-83; Boomsma *et al.*, 1995, *Clin. Sci.(Lond)* 88:675-679; Boomsma *et al.*, 1999, *Diabetologia* 42:233-237; Meszaros *et al.*, 1999, *Metabolism* 48:113-117; Salmi *et al.*, 2002, *Am J Pathol* 161:2255-2262) and type II diabetes (Boomsma *et al.*, 1999, *Diabetologia* 42:233-237; Garpenstrand *et al.*, 1999, *Diabet. Med.* 16:514-521; Meszaros *et al.*, 1999, *Metabolism* 48:113-117). The soluble form of VAP-1/SSAO enhances the binding capacity of lymphocytes to endothelial cells (Kurkijarvi *et al.*, 1998, *J Immunol.* 161:1549-1557) presumably through a lymphocyte preactivation signal. In addition, SSAO aldehyde products, such as formaldehyde or methylglyoxal, may generate protein cross-linking or AGE products implicated in atherogenic lesions, retinopathy and angiopathy associated with diabetes.

Because all these events can promote inflammation and atherosclerosis (Osterud & Bjorklid, 2003, *Physiol Rev.* 83:1069-1112), pharmacological inhibition of VAP-1/SSAO may reduce a variety of pathologies. A need exists, therefore, for inhibitors of SSAO/VAP-1 that can be used therapeutically to alleviate the symptoms and pathology associated with expression or over-expression of SSAO/VAP-1 in a number of disease states and other disorders.

SUMMARY OF THE INVENTION

The present invention provides SSAO/VAP-1 inhibitors having the general formula I:

$$R_3\text{-}(Y)_n\text{-}(CR_2R_2)_m\text{-}Z$$

or a pharmaceutically acceptable salt thereof, wherein

m is 0 or 1-6 (in another aspect, m is 0 or 1-4);

n is 0 or 1-6 (in another aspect, n is 0 or 1-4);

Z is $CONR_1OH$, COOH, $B(OH)_2$, SO_2NR_1OH, OR_1, SR_1, NHR_1, PO_3H, CH_2NHR_1, COR_1, $CONHR_1$, $CHNR_1$, or CNR_1NHR_1;

Y at each occurrence is independently –CO-, -CS-, $-NR_2OR_2$-, $-NR_2$-, $-SR_2$-, $-NR_2SO_2R_2$-, $-COR_2$-, $-NR_2$-$C(NR_2)$-NR_2-, –(C_1-C_6 alkyl)-NHC(O)-, –(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, -NHC(O)–(C_1-C_6 alkyl)-, -N(C_1-C_6 alkyl)C(O) –(C_1-C_6 alkyl)-, -NHC(O)-, -N(C_1-C_6alkyl)C(O)-, -C(O)NH-, -C(O)-N(C_1-C_6alkyl), $-SO_2NH$-, $-SO_2$-N(C_1-C_6alkyl)-, -(C_1-C_6 alkyl)-C(O)NH-, –(C_1-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, -O–(C_1-C_6 alkyl)-NHC(O)-, or -O–(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH, indolyl, pyrrolyl, pyridyl, furanyl, guanidinyl, carboxyl, or =O;

R_1 at each occurrence is independently H, C_1-C_6 alkyl, aryl, substituted aryl, heterocycloalkyl containing at least one and no more than two heteroatoms selected from S, N, and O, or C_3-C_7 cycloalkyl, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

R_2 at each occurrence is independently H, C_1-C_6 alkyl, carboxyl, C_1-C_6 alkoxycarbonyl, aryl, substituted aryl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, C_3-C_7 cycloalkylalkoxy, heteroaryl, heteroarylalkyl, heterocycloalkyl, or heterocycloalkylalkyl, where each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, substituted aryl, halogen, nitro, nitroso, aldehyde (CHO), carboxylic acid, $-C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl, -SH, or nitrile; and

R_3 is aryl, C_1-C_6 alkyl, C_2-C_4 alkenyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl C_1-C_6 alkyl, C_3-C_7 cycloalkyl C_1-C_6 alkoxy, heteroaryl, heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, nitro, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), CN, CO_2H, C_1-C_6 alkylthio, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_6 acyloxy, aryl, heteroaryl, or hydroxyl, where the aryl and heteroaryl substituents on R_3 are further optionally substituted with one or more groups that are

independently C_1-C_6 alkyl, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), OH, NO_2, C_1-C_6 alkoxy, halogen, arylalkoxy (in one aspect, phenylalkoxy, in another aspect, phenylC_1 alkoxy), haloalkyl (in one aspect, CF_3), haloalkoxy (in one aspect, OCF_3), thiol, or C_2-C_6 alkanoyl (in one aspect, C_2 alkanoyl).

The invention also provides methods for preparing a compound of formula I.

The invention further provides compounds of formula I prepared according to the methods of the invention.

The invention specifically provides methods for inhibiting SSAO/VAP-1 using the compounds of the invention.

The invention also provides pharmaceutical compositions comprising the SSAO/VAP-1 inhibitors of the invention and a pharmaceutically-acceptable diluent, solvent, excipient and/or adjuvant.

The invention further provides methods for treating a disease or disorder associated with SSAO/VAP-1 activity in an animal, wherein said SSAO/VAP-1 activity is inhibited in the animal, preferably by administering to the animal a compound or pharmaceutical composition of the SSAO/VAP-1 inhibitors of the invention. Preferably, the animal is a human.

Specific preferred embodiments of the present invention will become evident from the following more detailed description of certain preferred embodiments and the claims.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

As indicated above, the invention provides methods of preparing compounds of formula I, which are inhibitors of copper-containing amine oxidases (E.C. 1.4.3.6) including semicarbazide-sensitive amine oxidase (SSAO; also known as Vascular adhesion protein-1, VAP-1).

In one aspect, the invention provides compounds of formula I-a, i.e., compounds of formula I, or a pharmaceutically-acceptable salt thereof, wherein

Z is $CONR_1OH$, COOH, NHR_1, CH_2NHR_1, $CONHR_1$, or $CHNR_1$; wherein

R_1 at each occurrence is independently H, or C_1-C_6 alkyl, phenyl, naphthyl, binaphthyl, piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, S,S-dioxomorpholinyl, or C_3-C_7 cycloalkyl, where each of the above is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, phenyl, or naphthyl,

wherein the phenyl and naphthyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, amide, amine, C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl or nitrile.

In another aspect, the invention provides compounds of formula I-b, i.e., compounds of formula I, or a pharmaceutically-acceptable salt thereof, wherein

Y is –CO-, -COR_2-, –(C_1-C_6 alkyl)-NHC(O)-, –(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, -NHC(O)-, -N(C_1-C_6alkyl)C(O)-, -NHC(O)–(C_1-C_6 alkyl)-, -N(C_1-C_6 alkyl)C(O)–(C_1-C_6 alkyl)-, -C(O)NH-, -C(O)-N(C_1-C_6alkyl), -SO_2NH-, -SO_2-N(C_1-C_6alkyl)-, -(C_1-C_6 alkyl)-C(O)NH-, –(C_1-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, -O–(C_1-C_6 alkyl)-NHC(O)-, or -O–(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH, indolyl, pyrrolyl, pyridyl, furanyl, guanidinyl, carboxyl, or =O, wherein

R_2 at each occurrence is independently H, C_1-C_6 alkyl, phenyl, naphthyl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, C_3-C_7 cycloalkylalkoxy, pyridyl, thienyl, furanyl, imidazolyl, pyrimidyl, pyrrolyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, S,S-dioxomorpholinyl, piperidinyl C_1-C_4 alkyl, piperazinyl C_1-C_4 alkyl, pyrrolidinyl C_1-C_4 alkyl, morpholinyl C_1-C_4 alkyl, S,S-dioxomorpholinyl C_1-C_4 alkyl, where each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), amino, C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl or nitrile.

In still another aspect, the invention provides compounds of formula I-c, i.e., compound of formula I, or a pharmaceutically-acceptable salt thereof, wherein

R_3 is aryl, selected from phenyl, naphthyl, indanyl, and biphenyl, C_5-C_6 cycloalkyl, C_5-C_6 cycloalkyl C_1-C_6 alkyl, C_2-C_4 alkenyl, C_5-C_6 cycloalkyl C_1-C_6 alkoxy, heteroaryl, selected from pyridyl, pyrimidyl, indolyl, pyrrolyl, thienyl, furanyl, thiazolyl, pyrazolyl, and oxazolyl, heterocycloalkyl, selected from piperazinyl, piperidinyl, pyrrolidinyl, quinolinyl, isoquinolinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, and S,S-dioxothiomorpholinyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6

alkoxy, halogen, CF_3, OCF_3, nitro, CN, CO_2H, C_1-C_6 alkylthio, C_1-C_6 acyloxy, phenyl, pyridyl, thienyl, furanyl, pyrimidyl, or hydroxy.

In yet another aspect, the invention provides compounds of formula I-d, i.e., compounds of formula I, or a pharmaceutically-acceptable salt thereof, wherein

n is 1-4;

m is 1-4;

Z is $CONR_1OH$, COOH, NHR_1, CH_2NHR_1, $CONHR_1$, or $CHNR_1$; wherein

R_1 at each occurrence is independently H, or C_1-C_6 alkyl, phenyl, naphthyl, binaphthyl, piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, S,S-dioxomorpholinyl, or C_3-C_7 cycloalkyl, where each of the above is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, phenyl, or naphthyl, wherein the phenyl and naphthyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, halogen, nitro, carboxylic acid, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl or nitrile;

Y is –CO-, $-NR_2$-, $-COR_2$-, –(C_1-C_6 alkyl)-NHC(O)-, –(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, -NHC(O)-, -N(C_1-C_6alkyl)C(O)-, -C(O)NH-, -C(O)-N(C_1-C_6alkyl), $-SO_2NH$-, $-SO_2$-N(C_1-C_6alkyl)-, -(C_1-C_6 alkyl)-C(O)NH-, –(C_1-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, -O–(C_1-C_6 alkyl)-NHC(O)-, or -O–(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O; wherein

R_2 at each occurrence is independently H, C_1-C_6 alkyl, phenyl, naphthyl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, C_3-C_7 cycloalkylalkoxy, pyridyl, thienyl, furanyl, imidazolyl, pyrimidyl, pyrrolyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, S,S-dioxomorpholinyl, piperidinyl C_1-C_4 alkyl, piperazinyl C_1-C_4 alkyl, pyrrolidinyl C_1-C_4 alkyl, morpholinyl C_1-C_4 alkyl, S,S-dioxomorpholinyl C_1-C_4 alkyl, where each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6

alkyl)(C_1-C_6 alkyl), C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl, -SH, or nitrile; and

R_3 is aryl selected from phenyl, naphthyl, indanyl, and biphenyl, C_5-C_6 cycloalkyl, heteroaryl selected from pyridyl, pyrimidyl, indolyl, pyrrolyl, thienyl, furanyl, thiazolyl, pyrazolyl, and oxazolyl, heterocycloalkyl selected from piperazinyl, piperidinyl, pyrrolidinyl, quinolinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, and S,S-dioxothiomorpholinyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, nitro, CN, CO_2H, C_1-C_6 alkylthio, C_1-C_6 acyloxy, phenyl, pyridyl, thienyl, furanyl, pyrimidyl, or hydroxy.

In another aspect, the invention provides compounds of formula I-e, i.e., compounds of formula I-d, or a pharmaceutically-acceptable salt thereof, wherein

Z is $CONR_1OH$, or NHR_1, wherein

R_1 at each occurrence is independently H, or C_1-C_6 alkyl, wherein the alkyl group is optionally substituted with halogen, or C_1-C_6 alkoxy, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, halogen, nitro, carboxylic acid, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl.

In another aspect, the invention provides compounds of formula I-f, i.e., compounds of formula I-c or I-d, or a pharmaceutically-acceptable salt thereof, wherein Z is $CONR_1OH$, and R_1 is H, or C_1-C_6 alkyl.

In yet another aspect, the invention provides compounds of formula I-g, i.e., compounds of formula I-c or I-d, or a pharmaceutically-acceptable salt thereof, wherein R_1 is H.

In still another aspect, the invention provides compounds of formula I-h, i.e., compounds of formula I-c or I-d, or a pharmaceutically-acceptable salt thereof, wherein R_1 is C_1-C_6 alkyl.

In still yet another aspect, the invention provides compounds of formula I-i, i.e., compounds of formula I-c or I-d, or a pharmaceutically-acceptable salt thereof, wherein Z is $CONHR_1$.

In yet still another aspect, the invention provides compounds of formula I-j, i.e., compounds of formula I-c or I-d, wherein R_2 is independently H, or C_1-C_6 alkyl, where the alkyl group is optionally substituted with one or two groups that are independently halogen,

C_1-C_4 alkoxy, phenyl, naphthyl, nitro, CHO, carboxyl, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl, C_1-C_6 alkoxycarbonyl, or nitrile.

In another aspect, the invention provides compounds of formula I-k, i.e., compounds of formula I-j, wherein one R_2 is H and the other is H or C_1-C_6 alkyl, where the alkyl group is optionally substituted with OH, NH_2, or SH.

In another aspect, the invention provides compounds of formula I-l, i.e., compounds of formula I, I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-I, I-j, or I-k, wherein Y is $-NR_2-$,$-(C_1$-C_6 alkyl)-NHC(O)-, $-(C_1$-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, -NHC(O)-, $-N(C_1$-C_6alkyl)C(O)-, -C(O)NH-, -C(O)-N(C_1-C_6alkyl), $-SO_2NH-$, $-SO_2$-N(C_1-C_6alkyl)-, $-(C_1$-C_6 alkyl)-C(O)NH-, or $-(C_1$-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In another aspect, the invention provides compounds of formula I-m, i.e., compounds of formula I-l, wherein Y is $-NR_2-$, -NHC(O)-, -C(O)NH-, $-SO_2NH-$, or $-(C_1$-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In another aspect, the invention provides compounds of formula I-n, i.e., compounds of formula I-m, wherein Y is $-NR_2-$.

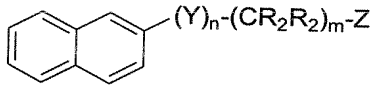
In another aspect, the invention provides compounds of formula I-o, i.e., compounds of formula I-m, wherein Y is --NHC(O)-.

In another aspect, the invention provides compounds of formula I-p, i.e., compounds of formula I-m, wherein Y is -C(O)NH-.

In another aspect, the invention provides compounds of formula I-q, i.e., compounds of formula I-m, wherein Y is $-SO_2NH-$.

In another aspect, the invention provides compounds of formula I-r, i.e., compounds of formula I-m, wherein Y is $-(C_1$-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, or 2 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In yet another aspect, the invention provides compounds of formula II, i.e., compounds of formula I-e, of the formula:



,

wherein Y, R_2, Z, n and m are as defined herein with regard to compounds of Formula I.

In another aspect, the invention provides compounds of formula II-a, i.e., compounds of formula II, or a pharmaceutically-acceptable salt thereof, wherein

Z is $CONR_1OH$, and

R_1 is independently H, or C_1-C_6 alkyl, wherein the alkyl group is optionally substituted with halogen, or C_1-C_6 alkoxy, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, halogen, nitro, carboxylic acid, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl.

In yet another aspect, the invention provides compounds of formula II-b, i.e., compounds of formula II-a, wherein n is 1 and m is 1, 2, or 3.

In yet another aspect, the invention provides compounds of formula II-c, i.e., compounds of formula II-b wherein Z is $CONR_1OH$, and R_1 is H.

In still yet another aspect, the invention provides compounds of formula II-d, i.e., compounds of formula II-b wherein Z is $CONR_1OH$, and R_1 is C_1-C_4 alkyl.

In still yet another aspect, the invention provides compounds of formula II-e, i.e., compounds according to any of formulas II, II-a, II-b, II-c, or II-d, wherein m is 1 or 2 and at least one R_2 is hydrogen.

In yet still another aspect, the invention provides a compound of formula II-f, i.e., compounds according to formula II-e, wherein Z is $CONR_1OH$, R_1 is H, and both R_2 groups are hydrogen.

In still yet another aspect, the invention provides compounds of formula II-g, i.e., compounds of formula II, or a pharmaceutically-acceptable salt thereof, wherein Z is $CONHR_1$.

In yet still another aspect, the invention provides compounds of formula II-h, i.e., compounds of formula II, II-a, II-b, II-c or II-d, wherein R_2 is independently H, or C_1-C_6 alkyl, where the alkyl group is optionally substituted with one or two groups that are independently halogen, C_1-C_4 alkoxy, phenyl, naphthyl, halogen, nitro, CHO, carboxyl,

$C(O)NH_2$, $C(O)NH(C_1\text{-}C_6$ alkyl), $C(O)N(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_6$ alkyl), NH_2, $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_6$ alkyl), hydroxyl, $C_1\text{-}C_6$ alkoxycarbonyl, or nitrile.

In another aspect, the invention provides compounds of formula II-i, i.e., compounds of formula II-h, wherein one R_2 is H and the other is H or $C_1\text{-}C_6$ alkyl, where the alkyl group is optionally substituted with OH, NH_2, or SH.

In another aspect, the invention provides compounds of formula II-j, i.e., compounds of formula II, II-a, II-b, II-c, II-d, II-e, II-f, II-g, II-h, or II-I, wherein Y is $-NR_2-$,–($C_1\text{-}C_6$ alkyl)-NHC(O)-, -($C_1\text{-}C_6$ alkyl)-N($C_1\text{-}C_6$ alkyl)C(O)-, -NHC(O)-, -N($C_1\text{-}C_6$alkyl)C(O)-, -C(O)NH-, -C(O)-N($C_1\text{-}C_6$alkyl), $-SO_2NH-$, $-SO_2$-N($C_1\text{-}C_6$alkyl)-, -($C_1\text{-}C_6$ alkyl)-C(O)NH-, or -($C_1\text{-}C_6$ alkyl)-C(O)-N($C_1\text{-}C_6$alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, $C_1\text{-}C_4$ alkoxy, amino, mono or di ($C_1\text{-}C_6$ alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In another aspect, the invention provides compounds of formula II-k, i.e., compounds of formula II-j, wherein Y is $-NR_2-$, -NHC(O)-, -C(O)NH-, $-SO_2NH-$, or -($C_1\text{-}C_6$ alkyl)-C(O)-N($C_1\text{-}C_6$alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, $C_1\text{-}C_4$ alkoxy, amino, mono or di ($C_1\text{-}C_6$ alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In another aspect, the invention provides compounds of formula II-n, i.e., compounds of formula II-k, wherein Y is $-NR_2-$.

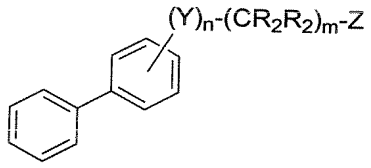
In another aspect, the invention provides compounds of formula II-o, i.e., compounds of formula II-k, wherein Y is --NHC(O)-.

In another aspect, the invention provides compounds of formula II-p, i.e., compounds of formula II-k, wherein Y is -C(O)NH-.

In another aspect, the invention provides compounds of formula II-q, i.e., compounds of formula II-k, wherein Y is $-SO_2NH-$.

In another aspect, the invention provides compounds of formula II-r, i.e., compounds of formula II-k, wherein Y is -($C_1\text{-}C_6$ alkyl)-C(O)-N($C_1\text{-}C_6$alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, or 2 groups that are independently halogen, $C_1\text{-}C_4$ alkoxy, amino, mono or di ($C_1\text{-}C_6$ alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In yet another aspect, the invention provides compounds of formula III, i.e., compounds of formula I-e, of the formula:



wherein Y, R_2, Z, n and m are as defined herein with regard to compounds of Formula I

In another aspect, the invention provides compounds of formula III-a, i.e., compounds of formula III, or a pharmaceutically-acceptable salt thereof, wherein

Z is $CONR_1OH$, and

R_1 is independently H, or C_1-C_6 alkyl, wherein the alkyl group is optionally substituted with halogen, or C_1-C_6 alkoxy, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, halogen, nitro, carboxylic acid, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl.

In yet another aspect, the invention provides compounds of formula III-b, i.e., compounds of formula III-a, wherein n is 1 and m is 1, 2,or 3.

In yet another aspect, the invention provides compounds of formula III-c, i.e., compounds of formula III-b wherein Z is $CONR_1OH$, and R_1 is H.

In still yet another aspect, the invention provides compounds of formula III-d, i.e., compounds of formula III-b wherein Z is $CONR_1OH$, and R_1 is C_1-C_4 alkyl.

In still yet another aspect, the invention provides compounds of formula III-e, i.e., compounds according to any of formulas III, III-a, III-b, III-c, or III-d, wherein m is 1 or 2 and at least one R_2 is hydrogen.

In yet still another aspect, the invention provides a compound of formula III-f, i.e., compounds according to formula III-e, wherein Z is $CONR_1OH$, R_1 is H, and both R_2 groups are hydrogen.

In still yet another aspect, the invention provides compounds of formula III-g, i.e., compounds of formula III, or a pharmaceutically-acceptable salt thereof, wherein Z is $CONHR_1$.

In yet still another aspect, the invention provides compounds of formula III-h, i.e., compounds of formula III, III-a, III-b, III-c or III-d, wherein R_2 is independently H, or C_1-C_6 alkyl, where the alkyl group is optionally substituted with one or two groups that are independently halogen, C_1-C_4 alkoxy, phenyl, naphthyl, halogen, nitro, CHO, carboxyl,

$C(O)NH_2$, $C(O)NH(C_1\text{-}C_6$ alkyl), $C(O)N(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_6$ alkyl), NH_2, $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_6$ alkyl), hydroxyl, $C_1\text{-}C_6$ alkoxycarbonyl, or nitrile.

In another aspect, the invention provides compounds of formula III-i, i.e., compounds of formula III-h, wherein one R_2 is H and the other is H or $C_1\text{-}C_6$ alkyl, where the alkyl group is optionally substituted with OH, NH_2, or SH.

In another aspect, the invention provides compounds of formula III-j, i.e., compounds of formula III, III-a, III-b, III-c, III-d, III-e, III-f, III-g, III-h, or III-I, wherein Y is $-NR_2-$, $-(C_1\text{-}C_6$ alkyl)-NHC(O)-, $-(C_1\text{-}C_6$ alkyl)-N($C_1\text{-}C_6$ alkyl)C(O)-, -NHC(O)-, $-N(C_1\text{-}C_6$alkyl)C(O)-, -C(O)NH-, $-C(O)\text{-}N(C_1\text{-}C_6$alkyl), $-SO_2NH-$, $-SO_2\text{-}N(C_1\text{-}C_6$alkyl)-, $-(C_1\text{-}C_6$ alkyl)-C(O)NH-, or $-(C_1\text{-}C_6$ alkyl)-C(O)-N($C_1\text{-}C_6$alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, $C_1\text{-}C_4$ alkoxy, amino, mono or di ($C_1\text{-}C_6$ alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In another aspect, the invention provides compounds of formula III-k, i.e., compounds of formula III-j, wherein Y is $-NR_2-$, -NHC(O)-, -C(O)NH-, $-SO_2NH-$, or $-(C_1\text{-}C_6$ alkyl)-C(O)-N($C_1\text{-}C_6$alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, $C_1\text{-}C_4$ alkoxy, amino, mono or di ($C_1\text{-}C_6$ alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In another aspect, the invention provides compounds of formula III-n, i.e., compounds of formula III-k, wherein Y is $-NR_2-$.

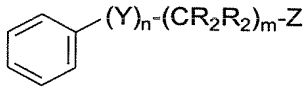
In another aspect, the invention provides compounds of formula III-o, i.e., compounds of formula III-k, wherein Y is --NHC(O)-.

In another aspect, the invention provides compounds of formula III-p, i.e., compounds of formula III-k, wherein Y is -C(O)NH-.

In another aspect, the invention provides compounds of formula III-q, i.e., compounds of formula III-k, wherein Y is $-SO_2NH-$.

In another aspect, the invention provides compounds of formula III-r, i.e., compounds of formula III-k, wherein Y is $-(C_1\text{-}C_6$ alkyl)-C(O)-N($C_1\text{-}C_6$alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, or 2 groups that are independently halogen, $C_1\text{-}C_4$ alkoxy, amino, mono or di ($C_1\text{-}C_6$ alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In yet another aspect, the invention provides compounds of formula IV, i.e., compounds of formula I-e, of the formula:



wherein Y, R_2, Z, n and m are as defined herein with regard to compounds of Formula I

In another aspect, the invention provides compounds of formula IV-a, i.e., compounds of formula IV, or a pharmaceutically-acceptable salt thereof, wherein

Z is $CONR_1OH$, and

R_1 is independently H, or C_1-C_6 alkyl, wherein the alkyl group is optionally substituted with halogen, or C_1-C_6 alkoxy, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, halogen, nitro, carboxylic acid, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl.

In yet another aspect, the invention provides compounds of formula IV-b, i.e., compounds of formula IV-a, wherein n is 1 and m is 1, 2, or 3.

In yet another aspect, the invention provides compounds of formula IV-c, i.e., compounds of formula IV-b wherein Z is $CONR_1OH$, and R_1 is H.

In still yet another aspect, the invention provides compounds of formula IV-d, i.e., compounds of formula IV-b wherein Z is $CONR_1OH$, and R_1 is C_1-C_4 alkyl.

In still yet another aspect, the invention provides compounds of formula IV-e, i.e., compounds according to any of formulas IV, IV-a, IV-b, IV-c, or IV-d, wherein m is 1 or 2 and at least one R_2 is hydrogen.

In yet still another aspect, the invention provides a compound of formula IV-f, i.e., compounds according to formula IV-e, wherein Z is $CONR_1OH$, R_1 is H, and both R_2 groups are hydrogen.

In still yet another aspect, the invention provides compounds of formula IV-g, i.e., compounds of formula IV, or a pharmaceutically-acceptable salt thereof, wherein Z is $CONHR_1$.

In yet still another aspect, the invention provides compounds of formula IV-h, i.e., compounds of formula IV, IV-a, IV-b, IV-c or IV-d, wherein R_2 is independently H, or C_1-C_6 alkyl, where the alkyl group is optionally substituted with one or two groups that are independently halogen, C_1-C_4 alkoxy, phenyl, naphthyl, halogen, nitro, CHO, carboxyl, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl, C_1-C_6 alkoxycarbonyl, or nitrile.

In another aspect, the invention provides compounds of formula IV-i, i.e., compounds of formula IV-h, wherein one R_2 is H and the other is H or C_1-C_6 alkyl, where the alkyl group is optionally substituted with OH, NH_2, or SH.

In another aspect, the invention provides compounds of formula IV-j, i.e., compounds of formula IV, IV-a, IV-b, IV-c, IV-d, IV-e, IV-f, IV-g, IV-h, or IV-I, wherein Y is -NR_2-, -(C_1-C_6 alkyl)-NHC(O)-, -(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, -NHC(O)-, -N(C_1-C_6alkyl)C(O)-, -C(O)NH-, -C(O)-N(C_1-C_6alkyl), -SO_2NH-, -SO_2-N(C_1-C_6alkyl)-, -(C_1-C_6 alkyl)-C(O)NH-, or -(C_1-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In another aspect, the invention provides compounds of formula IV-k, i.e., compounds of formula IV-j, wherein Y is -NR_2-, -NHC(O)-, -C(O)NH-, -SO_2NH-, or -(C_1-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In another aspect, the invention provides compounds of formula IV-n, i.e., compounds of formula IV-k, wherein Y is -NR_2-.

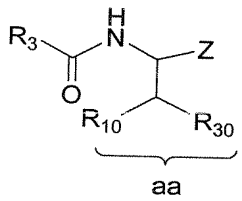
In another aspect, the invention provides compounds of formula IV-o, i.e., compounds of formula IV-k, wherein Y is --NHC(O)-.

In another aspect, the invention provides compounds of formula IV-p, i.e., compounds of formula IV-k, wherein Y is -C(O)NH-.

In another aspect, the invention provides compounds of formula IV-q, i.e., compounds of formula IV-k, wherein Y is -SO_2NH-.

In another aspect, the invention provides compounds of formula IV-r, i.e., compounds of formula IV-k, wherein Y is -(C_1-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, or 2 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH, indolyl, guanidinyl, carboxyl, or =O.

In certain other aspect, the invention provides compounds of formula B, wherein



aa: Different β-trifunctional amino acids, such as Ser, Thr, Cys and Dapa, with the exception of Gly. This function in the β position should be capable to chelate Cu^{2+} together with the hydroxamic acid.

Formula B

wherein n, R_3, and Z are as defined in Formula I;

R_{10} is H, alkyl optionally substituted with OH, SH, amino, NH(C_1-C_6 alkyl), or N(C_1-C_6 alkyl)(C_1-C_6 alkyl); and

R_{30} is H or C_1-C_4 alkyl (in one aspect, R_{30} is H; in another aspect, R_{30} is methyl).

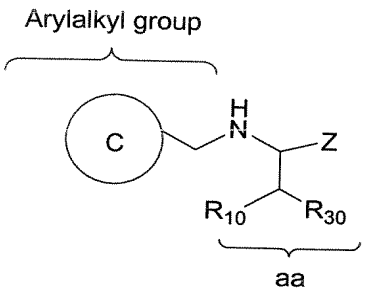
In another aspect, the invention provides compounds of formula B-1, i.e., compounds of formula B wherein R_3 is C_1-C_4 alkyl substituted with phenyl, where the phenyl is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkyl (in one aspect, C_1-C_4 alkyl, in another aspect, C_1-C_2 alkyl), OH, C_1-C_6 alkoxy, or phenyl; or R_3 is C_3-C_6 cycloalkyl optionally substituted with phenyl, where the phenyl is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkyl (in one aspect, C_1-C_4 alkyl, in another aspect, C_1-C_2 alkyl), OH, C_1-C_6 alkoxy, or phenyl.

In yet another aspect, the invention provides compounds of formula B-2, i.e., compounds of formula B wherein R_3 is C_2-C_3 alkenyl substituted with furanyl or phenyl, where the phenyl is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkyl (in one aspect, C_1-C_4 alkyl, in another aspect, C_1-C_2 alkyl), OH, C_1-C_6 alkoxy, or phenyl.

In still yet another aspect, the invention provides compounds of formula B-3, i.e., compounds of formula B wherein R_3 is indolyl, or phenyl, where the phenyl is optionally substituted with 1, 2, or 3 groups that are independently C_1-C_6 alkyl (in one aspect, C_1-C_4 alkyl, in another aspect, C_1-C_2 alkyl), OH, C_1-C_6 alkoxy, or phenyl.

In yet still another aspect, the invention provides compounds of formula B-4, i.e., compounds of formula B, B-1, B-2, or B-3, wherein Z is –C(O)NHOH.

In certain other aspect, the invention provides compounds of formula C, wherein



aa: Different β-trifunctional amino acids, such as Ser, Thr, Cys and Dapa, with the exception of Gly. This function in the β position should be capable to chelate Cu^{2+} together with the hydroxamic acid.

Arylalkyl groups: Introduced by reductive amination. Exploring its substitution on different positions (R_2 and R_3) with hydrophobic groups or groups capable to chelate Cu^{2+} together with the secondary amine.

Formula C

wherein Z is as defined in formula I;

R_{10} is H, amino, mono or di (C_1-C_6 alkyl)amino, OH, or SH;

R_{30} is H or C_1-C_4 alkyl (in one aspect, methyl); and

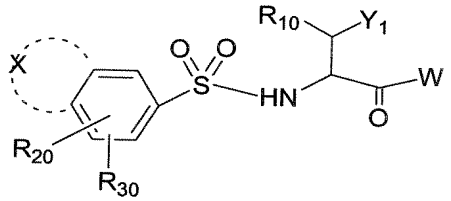
the C-ring is phenyl or naphthyl, each of which is optionally substituted with one ore more groups that are independently OH, NO_2, halogen (in one aspect, F), C_1-C_6 alkyl (in one aspect, methyl), C_1-C_6 alkoxy (in one aspect, methoxy), amino, mono or di (C_1-C_6 alkyl)amino, phenyl, phenyl C_1-C_4 alkoxy (in one aspect, benzyloxy).

In another aspect, the invention provides compounds of formula C-1, i.e., compounds of formula C, wherein the C-ring is phenyl optionally substituted with one ore more groups that are independently OH, NO_2, halogen (in one aspect, F), C_1-C_6 alkyl (in one aspect, methyl), C_1-C_6 alkoxy (in one aspect, methoxy), amino, mono or di (C_1-C_6 alkyl)amino, phenyl, phenyl C_1-C_4 alkoxy (in one aspect, benzyloxy).

In another aspect, the invention provides compounds of formula C-2, i.e., compounds of formula C, wherein the C-ring is naphthyl optionally substituted with one ore more groups that are independently OH, NO_2, halogen (in one aspect, F), C_1-C_6 alkyl (in one aspect, methyl), C_1-C_6 alkoxy (in one aspect, methoxy), amino, mono or di (C_1-C_6 alkyl)amino, phenyl, phenyl C_1-C_4 alkoxy (in one aspect, benzyloxy).

In another aspect, the invention provides compounds of formula C-3, i.e., compounds of formula C, wherein Z is C(O)NHOH.

In certain other aspect, the invention provides compounds of formula D, wherein



each R_{10} is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, substituted aryl, heterocycloalkyl containing at least one and no more than two heteroatoms selected from S, N, and O, or C_3-C_7 cycloalkyl, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

R_{20} and R_{30} are independently H, C_1-C_6 alkyl, aryl, substituted aryl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, C_3-C_7 cycloalkylalkoxy, heteroaryl, heteroarylalkyl, heterocycloalkyl, or heterocycloalkylalkyl, where each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, $-C(O)NH_2$, $-C(O)NH(C_1$-C_6 alkyl), $-C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), amino, mono or di (C_1-C_6 alkyl)amino, C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl or nitrile; and

W is NHOH, NH_2, NHR_{10}, OR_{10}, NH-NHR_{10};

X is C, CH, or any heteroatom selected from S, N, and O;

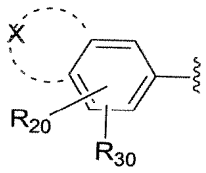
Y_1 is OR_{10}, NHR_{10}, or SR_{10};

the dashed lines represent a fused aryl or heterocycloalkyl ring that are optionally present.

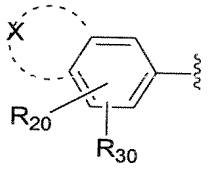
In another aspect, the invention provides compounds of formula D-1, i.e., compounds of formula D wherein R_{10} is H, C_1-C_6 alkyl.

In another aspect, the invention provides compounds of formula D-2, i.e., compounds of formula D-1 wherein Y_1 is OH, NH_2, or SH.

In another aspect, the invention provides compounds of formula D-3, i.e., compounds of formula D-2 wherein R_{20} and R_{30} are independently H, C_1-C_6 alkyl, phenyl, C_1-C_6 alkoxy, NO_2, CF_3, amino, mono or di (C_1-C_4 alkyl)amino.

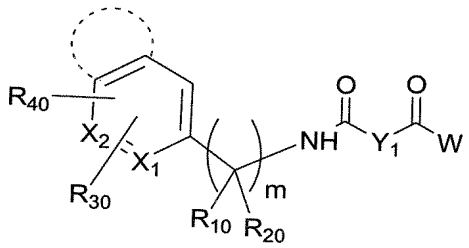
In another aspect, the invention provides compounds of formula D-4, i.e., compounds of formula D-3 wherein the 

portion of the molecule is a naphthyl group optionally substituted with R_{20} and R_{30}.

In another aspect, the invention provides compounds of formula D-5, i.e., compounds of formula D-3 wherein the  portion of the molecule is a quinolinyl group optionally substituted with R_{20} and R_{30}.

In another aspect, the invention provides compounds of formula D-6, i.e., compounds of formula D, D-1, D-2, D-3, D-4, or D-5, wherein W is NHOH.

In certain other aspect, the invention provides compounds of formula F, wherein



R_{10} and R_{20} are independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, substituted aryl, heterocycloalkyl containing at least one and no more than two heteroatoms selected from S, N, and O, or C_3-C_7 cycloalkyl, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

R_{30} and R_{40} are independently H, OH, SH, halogen, nitro, amino, mono or di(C_1-C_6 alkyl)amino, C_1-C_6 alkyl, C_1-C_6 alkanoyl, aryl, substituted aryl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, C_3-C_7 cycloalkylalkoxy, heteroaryl, heteroarylalkyl, heterocycloalkyl, or heterocycloalkylalkyl, where the cyclic portion, the alkyl portion or a combination thereof of each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), amino, mono or di(C_1-C_6 alkyl)amino, C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl or nitrile;

Y_1 is $(CH_2)_n$ or aryl;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

W is NHOH, NH_2, NHR_{10}, OR_{10}, or NH-NHR_{10};

X_1 and X_2 are independently C, CH, or N, provided that X_1 and X_2 are not simultaneously N; where the dashed lines represent a cycloalkyl or aryl group that is optionally present; and n and m independently an integer from 1 to 5.

In another aspect, the invention provides compounds of formula F-1, i.e., compounds of formula F, wherein m is 0.

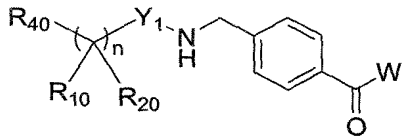
In yet another aspect, the invention provides compounds of formula F-2, i.e., compounds of formula F-1, wherein R_{30} and R_{40} are independently H, OH, SH, halogen, nitro, amino, mono or di(C_1-C_6 alkyl)amino, C_1-C_6 alkyl, C_1-C_6 alkanoyl, or C_1-C_6 alkoxy.

In still another aspect, the invention provides compounds of formula F-3, i.e., compounds of formula F-2, wherein Y_1 is $(CH_2)_n$, and n is 0, 1, or 2 (in one aspect, 2).

In yet still another aspect, the invention provides compounds of formula F-4, i.e., compounds of formula F-2, wherein Y_1 is phenyl, naphthyl, or biphenyl.

In yet still another aspect, the invention provides compounds of formula F-5, i.e., compounds of formula F-3, or F-4, wherein W is NHOH.

In certain other aspect, the invention provides compounds of formula I, wherein



R_{10} is independently H, C_1-C_6 alkyl, aryl, C_2-C_6 alkenyl, C_2-C_6alkynyl, substituted aryl, heterocycloalkyl containing at least one and no more than two heteroatoms selected from S, N, and O, or C_3-C_7 cycloalkyl, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

R_{20} and R_{40} are independently H, C_1-C_6 alkyl, aryl, substituted aryl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, C_3-C_7 cycloalkylalkoxy, heteroaryl, heteroarylalkyl, heterocycloalkyl, or heterocycloalkylalkyl, where each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, arylalkoxy (in one aspect, benzyloxy), substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), amino, C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl or nitrile; and

W is NHOH, NH_{20}, NHR_{10}, OR_{10}, NH-NHR_{10};

X is any heteroatom selected from S, N, and O; or

R_{10}, R_{20} and the carbon to which they are attached form a cycloalkyl ring (preferably C_5-C_6 cycloalkyl);

Y_1 is SO_2, C(O), CH_2, -NHC(O), and

n an integer from 1 to 5.

In another aspect, the invention provides compounds of formula I-1, i.e., compounds of formula I, wherein R_{40} is phenyl, naphthyl, furanyl, indolyl, or quinolinyl, where each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, halogen, nitro, carboxylic acid, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), amino, C_1-C_6 alkoxycarbonyl, hydroxyl or nitrile.

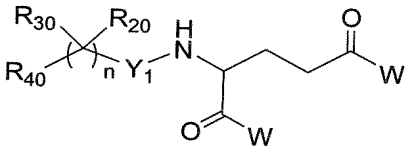
In yet still another aspect, the invention provides compounds of formula I-2, i.e., compounds of formula I-1, wherein n is 1 or 2 and R_{10} and R_{20} are both H.

In still yet another aspect, the invention provides compounds of formula I-3, i.e., compounds of formula I-1, wherein n is 0.

In another aspect, the invention provides compounds of formula I-4, i.e., compounds of formula I-1 or I-2, wherein W is NHOH.

In still yet another aspect, the invention provides compounds of formula I-5, i.e., compounds of formula I-1, wherein R_{10}, R_{20} and the carbon to which they are attached form a cycloalkyl ring (preferably C_5-C_6 cycloalkyl) and W is NHOH.

In certain other aspect, the invention provides compounds of formula J, wherein



R_{10} is independently H, C_1-C_6 alkyl, aryl, C_2-C_6 alkenyl, C_2-C_6alkynyl, substituted aryl, heterocycloalkyl containing at least one and no more than two heteroatoms selected from S, N, and O, or C_3-C_7 cycloalkyl, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

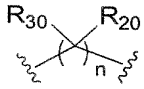
R_{20} is independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, substituted aryl, heterocycloalkyl containing at least one and no more than two heteroatoms selected from S, N, and O, or C_3-C_7 cycloalkyl, and where any member of the alkyl, aryl/or

cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

R_{30} and R_{40} are independently H, C_1-C_6 alkyl, aryl (in one aspect, phenyl), substituted aryl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, C_3-C_7 cycloalkylalkoxy, heteroaryl, heteroarylalkyl, heterocycloalkyl, or heterocycloalkylalkyl, where each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, -$C(O)NH_2$, -$C(O)NH(C_1$-C_6 alkyl), -$C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), amino, C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl or nitrile;

W at each occurrence is independently NHOH, NHR_{10}, OR_{10}, or NH-NHR_{10};

Y_1 is CH_2, C(O), or SO_2;



also encompasses olefins when n is at least 2, in such a case, R_{20} is not present on the olefinic carbons; or

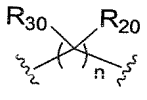
R_{20}, R_{30}, and the carbon to which they are attached form a cycloalkyl ring (in one aspect, a C_5-C_6 cycloalkyl ring) and

n is an integer from 1 to 5.

In another aspect, the invention provides compounds of formula J-1, i.e., compounds of formula J, wherein Y_1 is C(O).

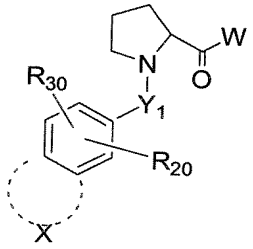
In yet another aspect, the invention provides compounds of formula J-2, i.e., compounds of formula J-1, wherein at least one W is OR_{10} (in one aspect, R_{10} is H or C_1-C_6 alkyl; in another aspect, both W groups are OH).

In still another aspect, the invention provides compounds of formula J-3, i.e., compounds of formula J-2, wherein R_{40} is phenyl, indolyl, or furanyl, where each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_6 alkyl (in one aspect, C_1-C_2 alkyl), C_1-C_6 alkoxy (in one aspect, C_1-C_2 alkoxy), aryl (in one aspect, phenyl), halogen, nitro, carboxylic acid, -$C(O)NH_2$, -$C(O)NH(C_1$-C_6 alkyl), -$C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), amino, C_1-C_6 alkoxycarbonyl, hydroxyl or nitrile.

In yet still another aspect, the invention provides compounds of formula J-4, i.e., compounds of formula J-3, wherein when n is 2;  is a C_2 olefin; R_{20} is absent and R_{30} is H or C_1-C_4 alkyl.

In still another aspect, the invention provides compounds of formula J-5, i.e., compounds of formula J-3, wherein R_{20}, R_{30}, and the carbon to which they are attached form a cycloalkyl ring (in one aspect, a C_5 cycloalkyl ring) and at least one W is OH (in another aspect, both W groups are OH).

In certain other aspect, the invention provides compounds of formula K, wherein



R_{20} and R_{30} are independently H, C_1-C_6 alkyl, aryl, substituted aryl, heterocycloalkyl containing at least one and no more than two heteroatoms selected from S, N, and O, or C_3-C_7 cycloalkyl, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, OH, SH, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl (in one aspect, phenyl) or substituted aryl;

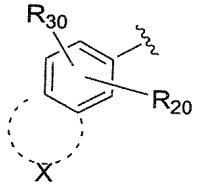
W is NHOH, NHR_{10}, OR_{10}, or NH-NHR_{10};

X is C, CH, or any heteroatom selected from S, N, and O;

Y_1 is CO, or CH_2; and

the dashed lines represent a fused heteroaryl or heterocycloalkyl ring, which is optionally present.

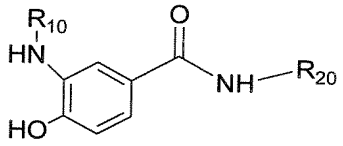
In another aspect, the invention provides compounds of formula K-1, i.e., compounds of formula K, wherein Y_1 is CO.

In still another aspect, the invention provides compounds of formula K-2, i.e., compounds of formula K-1, wherein  is phenyl, naphthyl, pyridyl, or

quinolinyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently OH, SH, C_1-C_4 alkyl, C_1-C_4 alkoxy, or phenyl.

In yet still another aspect, the invention provides compounds of formula K-2, i.e., compounds of formula K-1, wherein W is NHOH or NH_2.

In certain other aspect, the invention provides compounds of formula M, wherein

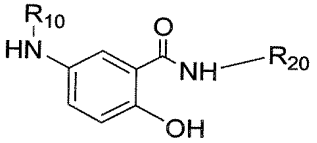


R_{10} and R_{20} are independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl (in one aspect, phenyl), substituted aryl, heterocycloalkyl containing at least one and no more than two heteroatoms selected from S, N, and O, or C_3-C_7 cycloalkyl, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl.

In another aspect, the invention provides compounds of formula M-1, i.e., compounds of formula M, wherein R_{10} is H or C_1-C_4 alkyl.

In still another aspect, the invention provides compounds of formula M-2, i.e., compounds of formula M-1, wherein R_{20} is C_1-C_6 alkyl substituted with phenyl or naphthyl, where the each is optionally substituted with 1 or 2 groups that are independently OH, halogen, C_1-C_4 alkyl (in one aspect, methyl), or C_1-C_4 alkoxy (in one aspect, methoxy).

In certain other aspect, the invention provides compounds of formula N, wherein



R_{10} and R_{20} are independently H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl (in one aspect, phenyl), substituted aryl, heterocycloalkyl containing at least one and no more than two heteroatoms selected from S, N, and O, or C_3-C_7 cycloalkyl, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl.

In another aspect, the invention provides compounds of formula N-1, i.e., compounds of formula N, wherein R_{10} is H or C_1-C_4 alkyl.

In still another aspect, the invention provides compounds of formula N-2, i.e., compounds of formula N-1, wherein R_{20} is C_1-C_6 alkyl substituted with phenyl or naphthyl, where the each is optionally substituted with 1 or 2 groups that are independently OH, halogen, C_1-C_4 alkyl (in one aspect, methyl), or C_1-C_4 alkoxy (in one aspect, methoxy).

Definitions

By "alkyl", and "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "alkoxy", and "C_1-C_6 alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

By "cycloalkyl", e.g., C_3-C_7 cycloalkyl, in the present invention is meant cycloalkyl groups having 3-7 atoms such as, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl, naphthyl, anthryl, or phenanthryl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl), where each aryl group is optionally mono-, di-, or trisubstituted with groups that are independently, e.g., halogen, NO_2, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, trifluoromethyl, C_1-C_6 acyloxy, aryl (in one aspect, phenyl), heteroaryl (in one aspect, pyridyl, indolyl, or furanyl), and hydroxy. Preferred aryl groups include phenyl, biphenyl, and naphthyl, each of which is optionally substituted as defined herein. More preferred aryl groups include phenyl and naphthyl, each of which is optionally substituted as defined herein.

By "heteroaryl" is meant an aromatic ring or aromatic ring system, wherein each ring contains of 5-, 6-, or 7-members wherein at least one and up to four ring members are

selected from nitrogen, oxygen, or sulfur, and where the heteroaryl group is optionally mono, di, or trisubstituted with groups that are independently, e.g., halogen, NO_2, amino, $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkylthio, trifluoromethyl, $C_1\text{-}C_6$ acyloxy, aryl (in one aspect, phenyl), heteroaryl (in one aspect, pyridyl, indolyl, or furanyl), and hydroxy. Such heteroaryl groups include, for example, thienyl, furanyl, thiazolyl, imidazolyl, (is)oxazolyl, pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrimidinyl, (iso)quinolinyl, indolyl, napthyridinyl, benzimidazolyl, and benzoxazolyl. Preferred heteroaryls are thiazolyl, pyrimidinyl, pyrimidin-2-yl, indolyl, pyridyl, 1-imidazolyl, 2-thienyl, 1-, or 2- quinolinyl, 1-, or 2- isoquinolinyl, 1-, or 2- tetrahydro isoquinolinyl, 2- or 3- furanyl, imidazolyl, and 2- tetrahydrofuranyl.

By "heterocycloalkyl," is meant one or more carbocyclic ring systems of 3, 4, 5, 6, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, and sulfur, and where each heterocycloalkyl group is where each aryl group is optionally mono-, di-, or trisubstituted with groups that are independently, e.g., halogen, NO_2, amino, $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_6$ alkyl), $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, $C_1\text{-}C_6$ alkylthio, trifluoromethyl, $C_1\text{-}C_6$ acyloxy, aryl (in one aspect, phenyl), heteroaryl (in one aspect, pyridyl, indolyl, or furanyl), and hydroxy. Preferred heterocycles of the present invention include morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, azepanyl, diazepanyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide.

Compounds of formula I are useful as pharmaceutical agents, and can be provided as pharmaceutical compositions. The pharmaceutical compositions can be manufactured in a manner that is itself known, *e.g.*, by means of a conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions can be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitic, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, $HOOC-(CH_2)_n-CH_3$ where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

For injection, the compounds prepared according to the methods of the invention can be formulated in appropriate aqueous solutions, such as physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal and transcutaneous administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well-known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which can optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate

and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions can take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds prepared according to the methods of the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of *e.g.*, gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyloleate or triglycerides, or liposomes. Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension can also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use. The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations can be administered by

implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for hydrophobic compounds of formula I is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system can be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycoL300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system can be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components can be varied: for example, other low-toxicity nonpolar surfactants can be used instead of polysorbate 80; the fraction size of polyethylene glycol can be varied; other biocompatible polymers can replace polyethylene glycol, *e.g.* polyvinyl pyrrolidone; and other sugars or polysaccharides can substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds can be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also can be employed, although usually at the cost of greater toxicity. Additionally, the compounds can be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules can, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein and nucleic acid stabilization can be employed.

The pharmaceutical compositions also can comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

The compounds of Formula I can be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, phosphoric, hydrobromic, sulfinic, formic, toluenesulfonic, methanesulfonic, nitic, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, $HOOC-(CH_2)_n-CH_3$ where n is 0-4, and the like. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

Pharmaceutical compositions of the compounds prepared according to the methods of the invention can be formulated and administered through a variety of means, including systemic, localized, or topical administration. Techniques for formulation and administration can be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA. The mode of administration can be selected to maximize delivery to a desired target site in the body. Suitable routes of administration can, for example, include oral, rectal, transmucosal, transcutaneous, or intestinal administration; potential delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections.

Alternatively, one can administer the compound in a local rather than systemic manner, for example, *via* injection of the compound directly into a specific tissue, often in a depot or sustained release formulation.

Pharmaceutical compositions suitable for use include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For administration to non-human animals, the drug or a pharmaceutical composition containing the drug may also be added to the animal feed or drinking water. It will be convenient to formulate animal feed and drinking water products with a predetermined dose of the drug so that the animal takes in an appropriate quantity of the drug along with its diet. It will also be convenient to add a premix containing the drug to the feed or drinking water approximately immediately prior to consumption by the animal.

Preferred compounds prepared according to the methods of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability, low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lives. Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová *et al.* (1996, *Journal of Chromatography B-Biomedical Applications* 677:1-28). Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (1998, *Drug Metabolism and Disposition* 26:1120-1127).

Toxicity and therapeutic efficacy of such compounds can be determined by conventional pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD_{50} and ED_{50}. Compounds that exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (*See, e.g.* Fing *et al.*, 1975, in THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Ch.1, p.1).

Dosage amount and interval can be adjusted individually to provide plasma levels of the active moiety that are sufficient to maintain bacterial cell growth-inhibitory effects. Usual patient dosages for systemic administration range from 100 - 2000 mg/day. Stated in terms of patient body surface areas, usual dosages range from 50 - 910 mg/m^2/day. Usual average plasma levels should be maintained within 0.1-1000 μM. In cases of local administration or selective uptake, the effective local concentration of the compound cannot be related to plasma concentration.

Compounds provided by the present invention are useful the treatment or prevention of a plurality of diseases and disorders caused by or associated with SSAO activity or inappropriate activity or expression thereof. Particular disorders include inflammatory

diseases, adipocyte dysfunction related diseases, carbohydrate metabolism related diseases, vascular diseases, neurodegenerative diseases or cancer. Said diseases and disorders include but are not limited to inflammatory disease including rheumatoid arthritis, osteoarthritis, spondylitis, bone resorption diseases, sepsis, septic shock, atherosclerosis, retinopathy, including diabetic retinopathy, diabetes, chronic pulmonary inflammatory disease, fever, periodontal diseases, ulcerative colitis, pyresis, Alzheimer's and Parkinson's diseases, cystic fibrosis, dysfunctions of the immune system, diabetes onset and maintenance of pancreatic function in diabetes. Preferred diseases and disorders include stroke, multiple sclerosis, migraine, cancer, pain. Generally, the compounds of the invention are provided to advantageously be used for treating or preventing inflammatory eye conditions including uveitis, glaucoma and conjunctivitis; degenerative bone or joint conditions including osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis ankylosing spondylitis, psoriatic arthritis and other arthritic conditions, as well as inflamed joints; chronic inflammatory skin conditions, including allergic lesions, lichen planus, pityriasis rosea, eczema, psoriasis, and dermatitis; diseases and disorders of the gastrointestinal tract, including inflammatory bowel disease, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, peptic ulceration, particularly irritable bowel syndrome, reflux oesophagitis, and damage to the gastrointestinal tract resulting from infections, *for example*, by *Helicobacter pylori*, or from treatments with non-steroidal anti-inflammatory drugs; inflammatory lung disorders such as asthma, bronchitis, particularly chronic obstructive pulmonary disease, farmer's lung, acute respiratory distress syndrome; bacteraemia, endotoxaemia (septic shock), aphthous ulcers, gingivitis, pyresis, particularly pain, including inflammatory pain, neuropathic pain, acute pain or pain of a central origin; meningitis and pancreatitis; and other conditions associated with inflammation; central nervous system inflammatory conditions and diseases, including multiple sclerosis, Alzheimer's disease, and ischaemia-reperfusion injury associated with ischemic stroke; vascular diseases, such as atheromatous and nonatheromatous arteriosclerosis, ischemic heart disease, and Raynaud's Disease and Phenomenon; diabetes and its complications such as microvascular and macrovascular diseases such as atherosclerosis, vascular retinopathies, nephropathies and neuropathies.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those

who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

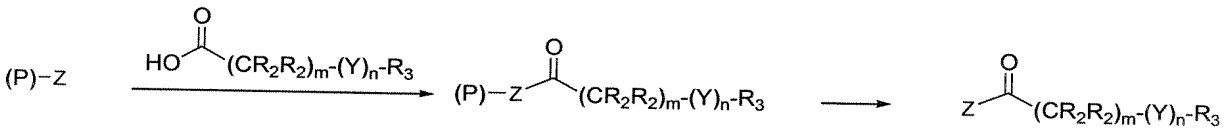
As used herein, the terms "treating" or "treatment" of a disease includes: (1) preventing the disease, *i.e.* causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease, (2) inhibiting the disease, *i.e.*, arresting or reducing the development of the disease or its clinical symptoms, or (3) relieving the disease, *i.e.*, causing regression of the disease or its clinical symptoms.

As used herein, the term "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, or other relevant characteristics of the mammal to be treated.

The compounds of the present invention may be prepared by use of known chemical reactions and procedures. Representative methods for synthesizing compounds of the invention are presented below. It is understood that the nature of the substituents required for the desired target compound often determines the preferred method of synthesis. All variable groups of these methods are as described in the generic description if they are not specifically defined below.

A first general method (Method I) for preparing the agents of formula (I) is summarized in Reaction Scheme 1.

Reaction Scheme I.



wherein R_1 can be H, C_1-C_6 alkyl, aryl/or substituted aryl, or cycloalkyl, /or where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl /members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

wherein R_2 can be H, C_1-C_6 alkyl, aryl/or substituted aryl, C_1-C_6 alkoxyalkyl, or cycloalkyl or cycloalkyl/alkoxy, where each cycloalkyl has from 3-7 members, where up to

two of the cycloalkyl members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl or cycloalkyl is optionally substituted with halogen, C_1-C_6 alkyl/or C_1-C_6 alkoxy, aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), C_1-C_6 alkoxycarbonyl, sulfate, phosphate, boronic acid, thio, oxime, or imino. Where R_2 is aryl or aryl fused ring (where up to two of the cycloalkyl members are optionally hetero atoms selected from sulfur, oxygen and nitrogen), R_2 can be further substituted in any position with halogen, nitro, nitroso, aldehyde, carboxylic acid, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), amino, C_1-C_6 alkoxycarbonyl, sulfate, phosphate, boronic acid, thio, oxime, imino, or hydroxyl; and

R_3 and Z are as defined in formula I.

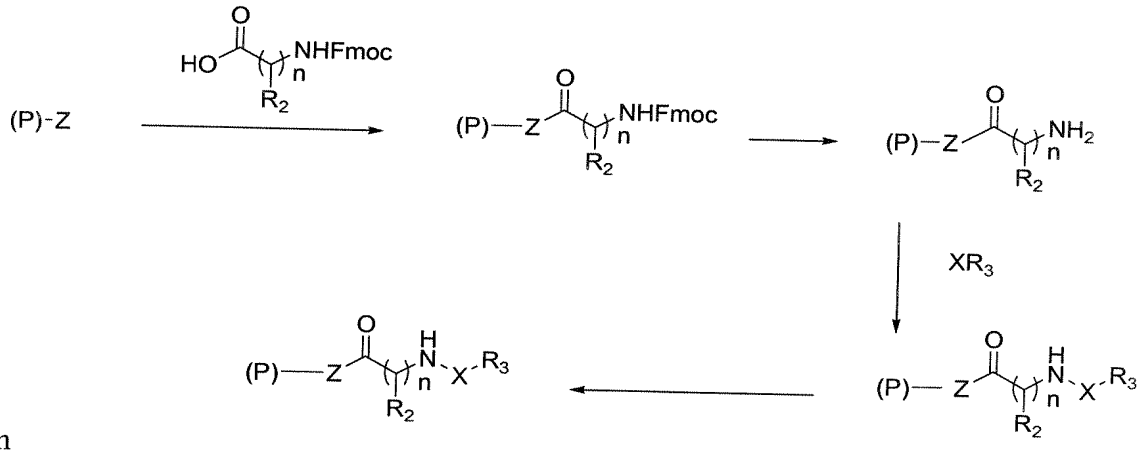
This reaction scheme comprises carrying out a condensation with a hydroxylamine group anchored onto a polymeric support (Z=NH R_1O), or Rink Amide (Z= NH_2), or Wang resin (Z=OH), or BAL resin (Z= NHR_1) including the following steps:

a) acylating with the corresponding acid (4 equiv.) the free amino function of the polymeric support using 4 equiv of the corresponding acylating mixture (*e.g.* HOBt/DIPCDI, HOAt/HATU/DIEA) in 1 mL of DMF at room temperature for 1h; and

b) releasing the compound of the polymeric support using 1 mL TFA in DCM.

A second general method (Method II) for preparing the agents of formula (I) is summarized in Reaction Scheme 2.

Scheme II



wherein

X can be SO_2 (sulfonyl derivatives), CO (acylated derivates), CH_2 (alkylated derivatives) or CONH (urea derivatives);

R_1 can be C_1-C_6 alkyl, aryl/or substituted aryl, or cycloalkyl/or where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl /members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

R_2 can be natural an non natural amino acids side chains;

n is an integer between 1 and 6;

R_3 can be C_1-C_6 alkyl, aryl/or substituted aryl, or cycloalkyl/ or cycloalkyl/alkoxy, where each cycloalkyl or aryl group has from 3-7 members, where up to two of the cycloalkyl/members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, alkylaryl , alkylaryl fused ring or cycloalkyl/group and alkylaryl is optionally substituted with halogen, C_1-C_6 alkyl/or C_1-C_6 alkoxy, aryl or substituted aryl, arylfused ring, halogen, nitro, nitroso, aldehyde, carboxylic acid, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), amino, C_1-C_6 alkoxycarbonyl, or sulfate, phosphate, boronic acid, thio, oxime, imino, hydroxyl., or nitrile.

Z is defined in formula I.

The method of scheme 2 comprises carrying out a condensation with a hydroxylamine group anchored onto a polymeric support (Z=NHR_1O), or Rink Amide (Z= NH_2), or Wang resin (Z=OH), or BAL resin (Z= NHR_1) including the following steps:

a) coupling the amino acid (4 equiv) with the free amino function of the polymeric support using 4 equiv of the corresponding acylating mixture (*e.g.*. HOBt/DIPCDI, HOAt/HATU)in 1 mL of DMF at room temperature for 1 h;

b) removing the protecting group (*e.g.*, 9-fluorenylmethoxycarbonyl) with two treatments of 15 min with 1 ml of piperidine/DMF (50:50) at room temperature ;

c1) for sulfonylation: reacting 5 equiv of the corresponding sulfonyl chloride in 1 mL of DCM and 5 equiv. of DIEA at room temperature for 12 h with the free amino function of the amino acid;

c2) for acylation: reacting 3 equiv of the corresponding acid with 3 equiv of HOBt/DIPCDI in 1 mL of DMF as acylating mixture at room temperature for 2 h with the free amino function of the amino acid;

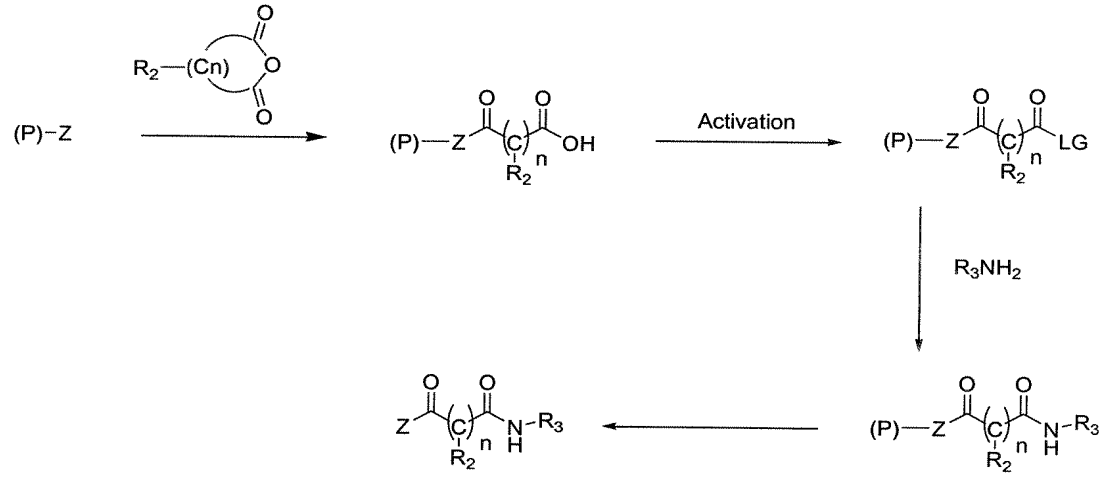
c3) for reductive amination: reacting 5 equiv of the corresponding aldehyde and 5 equiv of $NaBH_3CN$ in 1 mL of AcOH/DMF (1: 99) for 3 h at room temperature with the free amino function of the amino acid;

c4) for urea formation (two steps procedure): (a) carbamate formation by reacting 5 equiv of 4-nitrophenil chloroformate and 5 equiv of DIEA in 1 mL of DCM for 12 h at 60°C with the free amino function of the amino acid, and (b) urea formation by reacting 5 equiv of amine with 5 equiv of TEA in 1 mL of NMP for 12 h at 60°C.

d) releasing the compound of the polymeric support in acidic conditions using 1 mL of TFA in DCM.

A third general method (Method III) for preparing the agents of formula (I) is summarized in Reaction Scheme 3.

Reaction Scheme 3



wherein

R_1 can be C_1-C_6 alkyl, aryl/or substituted aryl, or cycloalkyl/or where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl/members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

wherein n is an integer between 1-6;

R_2 can be H, C_1-C_6 alkyl, aryl/or substituted aryl, biphenyl or cycloalkyl /or where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl/members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl/or cycloalkyl/group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

R_3 can be C_1-C_6 alkyl, aryl/or substituted aryl, or cycloalkyl/ or cycloalkyl/alkoxy, where each cycloalkyl/group has from 3-7 members, where up to two of the

cycloalkyl/members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, alkylaryl , alkylaryl fused ring or cycloalkyl/group and alkylaryl is optionally substituted with halogen, C_1-C_6 alkyl/or C_1-C_6 alkoxy, aryl or substituted aryl, arylfused ring, halogen, nitro, nitroso, aldehyde, carboxylic acid, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), C_1-C_6 alkoxycarbonyl, or sulfate, phosphate, boronic acid, thio, oxime, imino, hydroxyl., or nitrile.

Z is defined in formula I.

The method of Scheme 3 comprises carrying out a condensation with a hydroxylamine group anchored onto a polymeric support (Z=NHR_1O), or Rink Amide (Z= NH_2), or Wang resin (Z=OH), or BAL resin (Z= NHR_1) including the following steps:

a) overnight acylation of the free amino function of the polymeric support with 5 equiv of the corresponding anhydride in 1 mL of THF at 60°C;

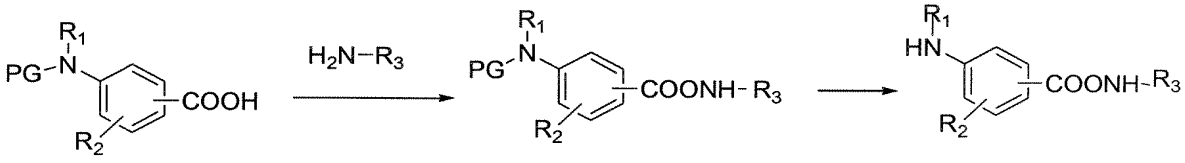
b) free acid activation with 25 equiv of CDI in 1 mL of DMF for 30 min ;

c) coupling the corresponding amine with 3 equiv of HOBt in 1 mL of DMF for 2 h at room temperature ; and

d) releasing the compound from the polymeric support in acidic conditions using 1 mL of % TFA in DCM.

A fourth general method (Method IV) for preparing the agents of formula (I) in solution phase is summarized in Reaction Scheme IV.

Scheme IV



wherein

R_1 can be C_1-C_6 alkyl, aryl/or substituted aryl, or cycloalkyl/or where each cycloalkylgroup has from 3-7 members, where up to two of the cycloalkyl/members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

wherein n is an integer between 1-6;

R_2 can be H, C_1-C_6 alkyl, aryl/or substituted aryl, or cycloalkyl/ or cycloalkyl/alkoxy, where each cycloalkyl/group has from 3-7 members, where up to two of the cycloalkyl/members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, alkylaryl, alkylaryl fused ring or cycloalkyl/group and alkylaryl is optionally substituted with halogen, C_1-C_6 alkyl/or C_1-C_6 alkoxy, aryl or substituted aryl, arylfused ring, halogen, nitro, nitroso, aldehyde, carboxylic acid, -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)N(C_1-C_6 alkyl)(C_1-C_6 alkyl), C_1-C_6 alkoxycarbonyl, or sulfate, phosphate, boronic acid, thio, oxime, , imino, hydroxyl., or nitrile.

R_3 can be C_1-C_6 alkyl, aryl/or substituted aryl, or cycloalkyl/or where each cycloalkyl group has from 3-7 members, where up to two of the cycloalkyl /members are optionally hetero atoms selected from sulfur, oxygen and nitrogen, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl; and

PG is Boc, Alloc, F-moc, Bz or any suitable protecting group;

The method of Scheme 4 comprises carrying out a condensation between an amine and carboxylic acid in solution phase, including the following steps:

a) reacting 1 equiv of the corresponding acid with 3 equiv of R_3NH_2/HOBt/DIPCDI in 1.5 mL of DMF as acylating mixture at room temperature for 2 h at room temperaure;

b) drying and purification by normal phase, ISOLUTE HM-N 3.0 cartridge or DIAION HP-20 ;

b) releasing the protecting group following standard procedures (e.g. acidic conditions using 1 mL of HCl/Dioxane 4 M for Boc protecting groups);

The following abbreviations are used herein:

ACN, acetonitrile;

Alloc, allyloxycarbonyl

Boc, *t*-butyloxycarbonyl

Bz, benzyl

TFA, trifluoroacetic acid;

THF, tetrahydrofurane;

MeOH, methanol;

F-moc, 9-fluorenylmethyloxycarbonyl;

DMF, dimethylformamide;

DCM, methylenechlorode;

DIEA, N,N-diisopropylethylamine;

CDI, 1,1'-carbonyldiimidazole;

HOBt, 1-hydroxybenzotriazole;

HOAt, 1-Hydroxy-7-azabentriazole;

DIPCDI, N,N'-diisopropylcarbodiimide;

HATU,(N-dimethylamino)-1H-1,2,3-triazolo(4,5-b)pyridine-1-ylmethylene)-N-ethylmethanominium hexafluorophosphate N-oxide;

Cl-Trt, chlorotrityl resin

ESI-MS, Electrospray ionization mass spectroscopy;

IR, infrared spectroscopy;

HPLC, high performance liquid chromatography;

t_R, retention time;

NMR, nuclear magnetic resonance;

LG; leaving group;

PG; Protecting Group; and

NMP, N-methylpyrrolidone.

Solid-phase manipulations were performed in polypropylene syringes fitted with a polyethylene porous disc. Solvents and soluble reagents were removed by filtration.

Representative compounds prepared according to the methods of the present invention include, but are not limited to the compounds disclosed herein and their pharmaceutically acceptable acid and base addition salts. In addition, if a compound is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The following Examples are provided for the purposes of illustration and are not intended to limit the scope of the present invention. The present invention is not to be limited in scope by the exemplified embodiments, which are intended as illustrations of individual aspects of the invention. Indeed, various modifications of the invention in addition to those

shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

EXAMPLES

Compounds obtained by Method I

General Experimental Procedure. Hydroxylamine Cl-Trt resin (100 mg, 0.8 mmol/gr) was acylated with carboxylic acid (4 equiv) and 4 equi. of the acylating mixture HATU/HOBT/DIEA (1:1:2) in DMF (1 mL) as for 1 h at room temperature. The resin was filtered off and washed with 1 mL of DMF (5x1 min) and 1 mL of DCM (5x1 min). The corresponding hydroxamic acid was cleaved with 1 mL 5 % of TFA in DCM (3x1 min) and dried. The crude material was dissolved in water and was purified using Diaion HP-20 (500 mg) following standard procedure. HPLC analyses were performed using the following eluent solutions: H_2O (0.1% HCOOH)/ACN(0.07% HCOOH) in a gradient from 0%-100% ACN over 10 min., using an X-Terra C_{18} 5μm column (4.6x100) and interrogating the column fractions spectrophotometrically (λ =220/254 nm).

DIAION HP-20 purification.

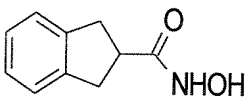
(a) 500 mg of DIAION HP-20 in polypropylene syringes fitted with a polyethylene porous disc were conditioned with three fractions of 10 mL MeOH and with three fractions of 10 mL water;

(b) the crude material was dissolved in 5 mL water and the aqueous fraction was eluted trough the resin;

(c) the resin was washed with 3 fractions of 10 mL water;

(d) the product was eluted with three fractions of 10 mL ACN and the solvent was evaporated.

Table of compounds obtained by Method

Ref. N°	Structure	Mol. Weight	% HPLC Purity	MS exp
2		177	80	178.1

Ref. N°	Structure	Mol. Weight	% HPLC Purity	MS exp
	N-hydroxyindane-2-carboxamide			

Compounds obtained by Method II

A. <u>Sulfonylated hydroxamic acid derivative compounds</u>

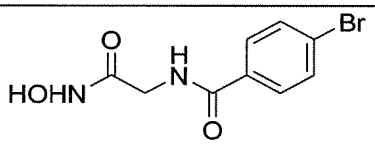
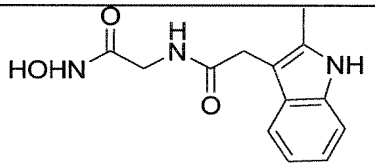
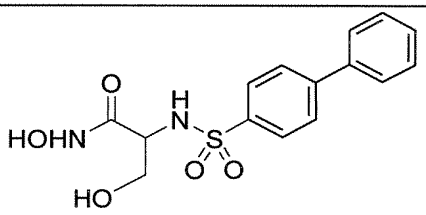
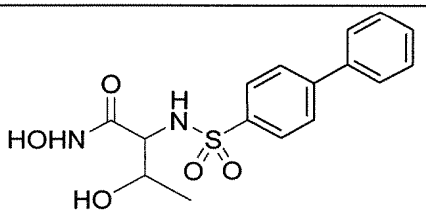
General Experimental Procedure. Hydroxylamine Cl-Trt resin (100 mg, 0.8 mmol/gr) was acylated with Fmoc amino acid (4 equivalents) and 4 equiv. of the acylating mixture HATU/HOBT/DIEA (1:1:2) in 1mL of DMF for 1 h at room temperature. The Fmoc group was then removed by treating with 1 mL of 50 % piperidine in DMF (three times for 10 min apiece), and the free amine was sulfonylated overnight with biphenylsulfonyl chloride (5 equiv) in 1mL of DCM. The resin was filtered off and washed with 1 mL of DCM (5 washes for 1 min apiece) and the extent of the reaction was checked by the ninhydrin test. The corresponding product was cleaved with 1 mL of 5 % TFA in DCM (3 treatments for 1 min apiece) and dried. The crude material was dissolved in water and was purified using Diaion HP-20 (500 mg) following standard procedures as disclosed above. The acetonitrile fraction was dried under vacuum. HPLC analyses were performed using the following eluent solutions: H_2O (0.1% HCOOH)/ACN(0.07% HCOOH) in a gradient from 0%-100% ACNover 10 min., using an X-Terra C_{18} 5μm column (4.6x100) and interrogating the column fractions spectrophotometrically (λ =220/254 nm).

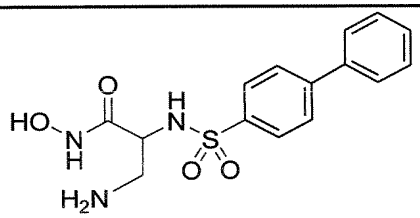
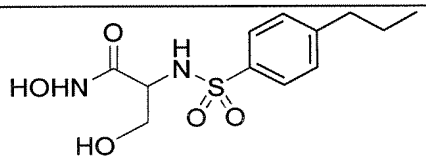
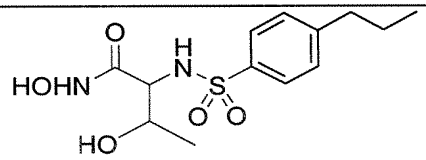
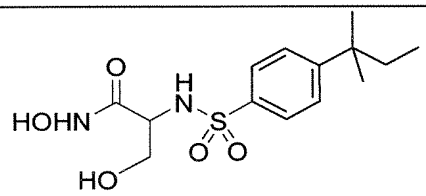
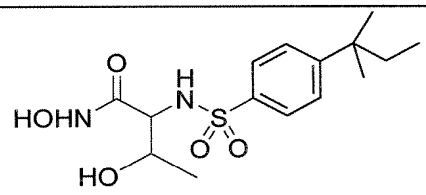
B. <u>Acylated hydroxamic acid derivatives compounds</u>.

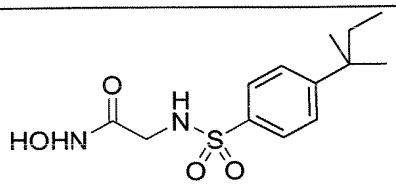
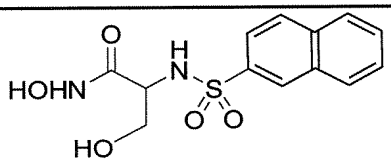
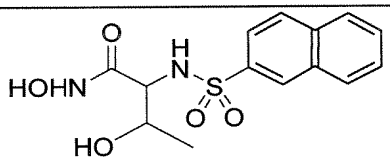
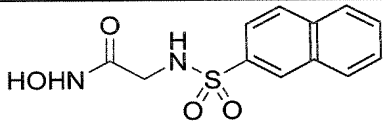
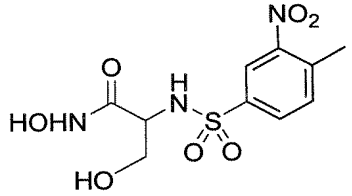
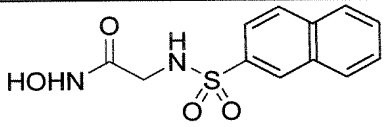
General Experimental Procedure. Hydroxylamine Cl-Trt resin (100 mg, 0.8 mmol/gr) was acylated with Fmoc amino acid (4 equiv.) and 4 equiv. of the acylating mixture HATU/HOBT/DIEA (1:1:2) in 1 mL of DMF for 1 h at room temperature. The Fmoc group was then removed by treating with 50% piperidine in 1 mL of DMF (10 x 3 min.), and the free amine was acylated with the corresponding carboxylic acid (3 equiv.) and 3 equiv. of the acylating mixture HOBT/DIPCDI (1:1) in 1 mL of DMF for 2 h at room temperature. The resin was filtered off and washed with 1 mL of DCM (5x1 min) and the extent of the reaction was determined using the ninhydrin test (Kaiser *et al.*, **1970**, *Analytical Biochem.*, 34:595-598). The corresponding product was cleaved with 1 mL of 5% TFA in DCM (3x1 min) and

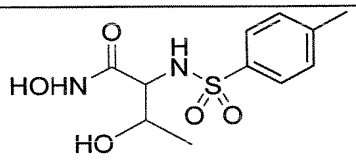
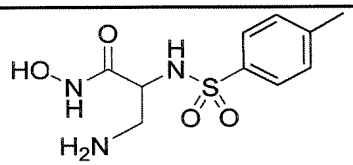
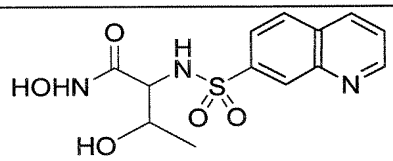
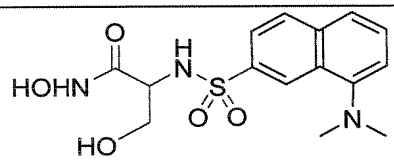
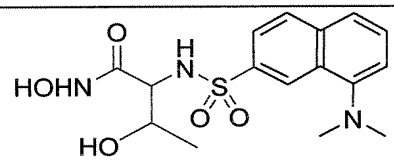
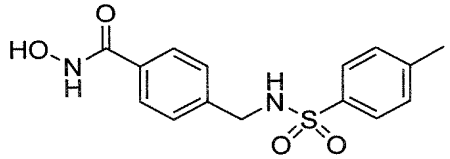
dried. The crude material was dissolved in water and was purified using Diaion HP-20 (500 mg) following standard procedures as disclosed above. The acetonitrile fraction was dried under vacuum. HPLC analyses were performed using the following eluent solutions: H_2O (0.1% HCOOH)/ACN(0.07% HCOOH) in a gradient from 0%-100% ACN over 10 min., using an X-Terra C_{18} 5μm column (4.6x100) and interrogating the column fractions spectrophotometrically (λ =220/254 nm).

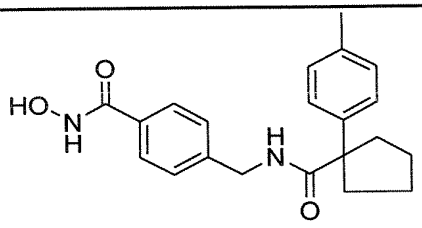
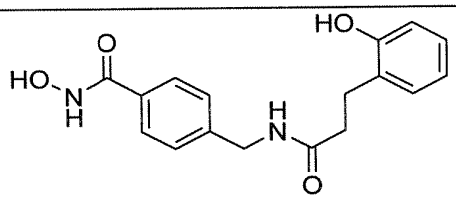
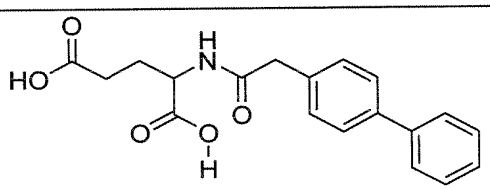
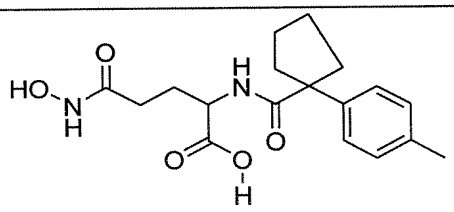
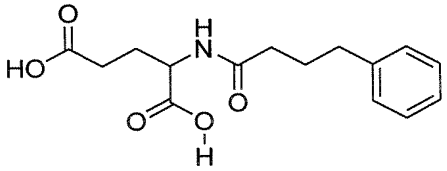
Table of compounds obtained by Method II

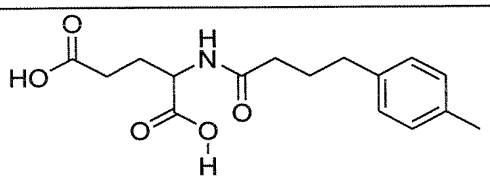
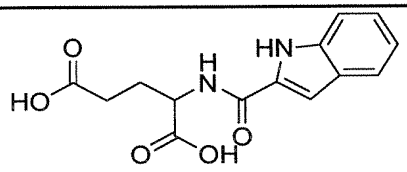
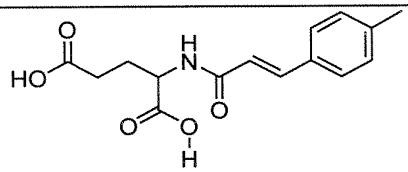
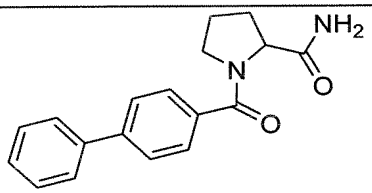
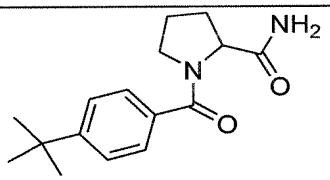
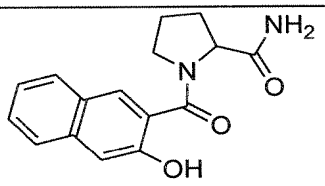
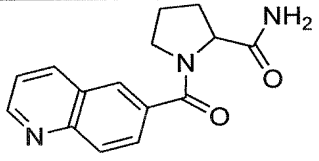
Ref. N°	Structure	Mol. Weight	% HPLC Purity	MS exp
3	 N^1-hydroxy-N^2-[(4-bromophenyl)carbonyl]glycinamide	272	90	273.8
4	 N-hydroxy-2-(2-(2-methyl-1H-indol-3-yl)acetamido)acetamide	260	83	261
5	 N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxyserinamide	336	81	337.1
6	 N^2-(biphenyl-4-ylsulfonyl)-N^1-	350	70	351.1

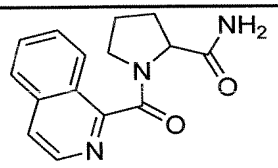
	hydroxythreoninamide			
7	 3-amino-N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxyalaninamide	335	84	335
8	 N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]serinamide	302	71	303.1
9	 N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]threoninamide	316	66	317.2
10	 N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxyserinamide	330	62	331.2
11	 N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxythreoninamide	344	68	345

12	 N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxyglycinamide	300	81	300.1
13	 N^1-hydroxy-N^2-(2-naphthylsulfonyl)serinamide	310	71	311.1
14	 N^1-hydroxy-N^2-(2-naphthylsulfonyl)threoninamide	324	86	325.2
15	 N^1-hydroxy-N^2-(2-naphthylsulfonyl)glycinamide	280	80	281
16	 N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]serinamide	310	77	311.1
17	 N^1-hydroxy-N^2-(2-naphthylsulfonyl)glycinamide	280	80	281

18	 N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]threoninamide	287	85	289.1
19	 3-amino-N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]alaninamide	273	95	273
20	 N^1-hydroxy-N^2-(quinolin-7-ylsulfonyl)threoninamide	325	70	326.6
21	 N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxyserinamide	352	60	353.1
22	 N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxythreoninamide	327	68	368.1
23	 *N*-hydroxy-4-({[(4-methylphenyl)sulfonyl]amino}methyl)benz	320	63	321

	amide			
24	 *N*-hydroxy-4-[({[1-(4-methylphenyl)cyclopentyl]carbonyl}amino)methyl]benzamide	352	78	353.1
25	 *N*-hydroxy-4-({[3-(2-hydroxyphenyl)propanoyl]amino}methyl)benzamide	314	71	315.1
26	 *N*-(biphenyl-4-ylacetyl)glutamic acid	341	70	293.1
27	 N^5-hydroxy-N^2-{[1-(4-methylphenyl)cyclopentyl]carbonyl}glutamine	348	70	351.2
28	 *N*-(4-phenylbutanoyl)glutamic acid	293	83	294.1

29	 *N*-[4-(4-methylphenyl)butanoyl]glutamic acid	307	73	308.2
30	 *N*-(1*H*-indol-2-ylcarbonyl)glutamic acid	290	51	291.2
31	 *N*-[(2*E*)-3-(4-methylphenyl)prop-2-enoyl]glutamic acid	291	74	292.1
32	 1-(biphenyl-4-ylcarbonyl)prolinamide	294	87	286.1
33	 1-(4-*tert*-butylbenzoyl)prolinamide	274	95	270.1
34	 1-(3-hydroxy-2-naphthoyl)prolinamide	284	90	286.1
35		269	94	270.1

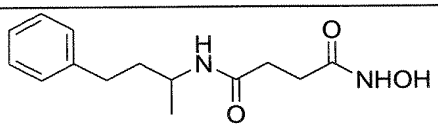
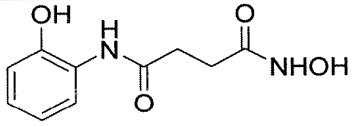
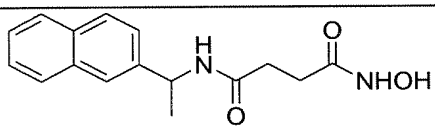
	1-(quinolin-6-ylcarbonyl)prolinamide			
36	 1-(isoquinolin-1-ylcarbonyl)prolinamide	269	90	271

C. Compounds obtained by Method III

General Experimental Procedure. Hydroxylamine Cl-Trt resin (100 mg, 0.8 mmol/gr) was acylated overnight with succínic anhydride (5 equiv) in THF at 60 °C. The resin was filtered off and washed with 1 mL of THF (5x1 min) and 1 mL of DCM (5x1 min) and the extent of the reaction was determined by the ninhydrin test as disclosed above. The carboxyl group was then activated with DIC (25 equiv) in 1 mL of DMF for 30 min. at 25 °C. The resin was filtered off and washed with 1 mL of DMF (5x1 min). Afterwards, the corresponding amine (3 equiv) and HOBt (3 equiv) in 1 mL of DMF were added and the mixture was stirred for 2 h at room temperature. The resin was filtered off and washed with 1 mL of THF (5x1 min) and 1 mL of DCM (5x1 min), and the extent of the reaction was checked by the malachite green test (Attardi *et al.*, 2000, *Tetrahedron Lett.*, 41: 7391-7394). The corresponding succinic derivative was cleaved with 1 mL of 5 % TFA in DC (3x1 min) and dried. The crude material was dissolved in water and was purified using Diaion HP-20 (500 mg) following standard procedures as described above. The acetonitrile fraction was dried under vacuum. HPLC analyses, which were performed using the following eluent solutions: H_2O (0.1% HCOOH)/ACN(0.07% HCOOH) in a gradient from 0%-100% ACN over 10 min., using an X-Terra C_{18} 5μm column (4.6x100) and interrogating the column fractions spectrophotometrically (λ =220/254 nm).

Table of compounds obtained by Method III

Ref. N°	Structure	Mol. Weight	% HPLC Purity	MS exp

Ref. Nº	Structure	Mol. Weight	% HPLC Purity	MS exp
37	 *N*-hydroxy-*N'*-(1-methyl-3-phenylpropyl)succinamide	264	80	265.3
38	 *N*-hydroxy-*N'*-(2-hydroxyphenyl)succinamide	224	85	225.1
39	 N1-hydroxy-N4-(1-(naphthalen-2-yl)ethyl)succinamide	286	86	287.2

D. <u>Compounds obtained by method IV</u>

General experimental Procedure.

A mixture of of 4-tert-Butoxycarbonylamino-3-hydroxy-benzoic acid (1 equiv), HOBt (1 equiv), 1 equiv of the corresponding amine R_3NH2 and 1 equiv DIPCDI was stirring in DMF (1.5 mL) overnight at room temperature. DMF was eliminated at low pressure and the crude and was purified using the ISOLUTE HM-N 3.0 cartridge and DIAION HP-20 following the standard procedures. Boc protecting group was removal with 1 mL of HCl/Dioxane 4.0 M treatment for a 1 h at room temperature. HPLC analyses were performed using the following eluent solutions: H_2O (0.1% HCOOH)/ACN(0.07% HCOOH) in a gradient from 0%-100% ACN over 10 min., using an X-Terra C_{18} 5μm column (4.6x100) and interrogating the column fractions spectrophotometrically (λ =220/254 nm).

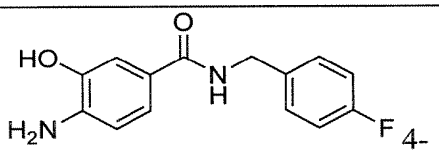
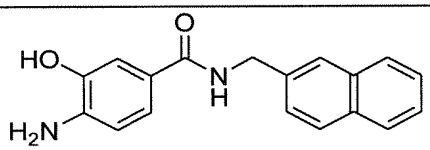
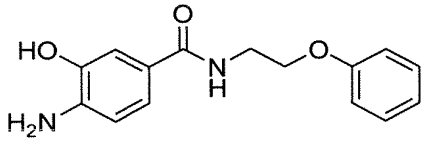
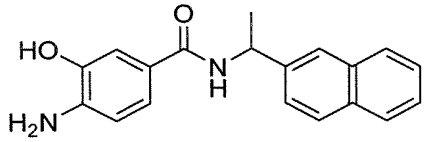
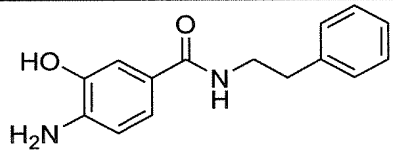
ISOLUTE HM-N 3.0 cartridge

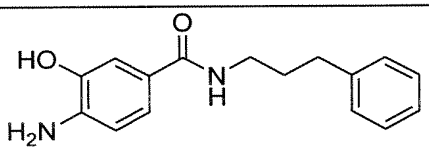
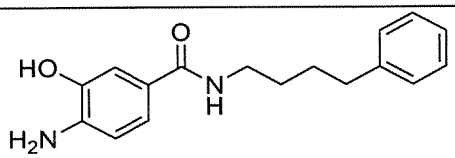
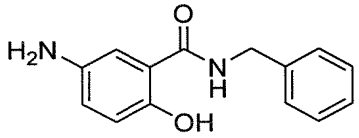
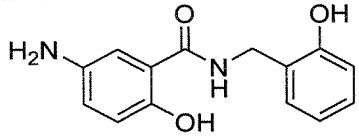
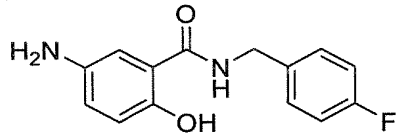
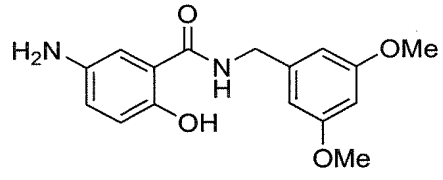
(a) crude material was dissolved in 1.5 mL of 5 % $NaHCO_3$ and 1.5 mL of ethyl acetate and was eluted trough the cartridge;

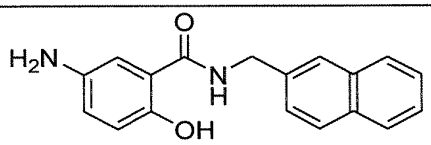
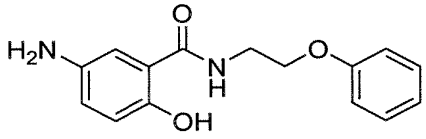
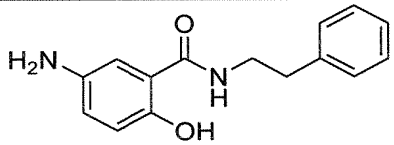
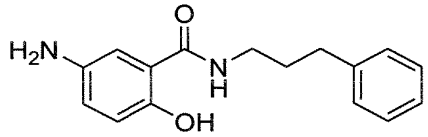
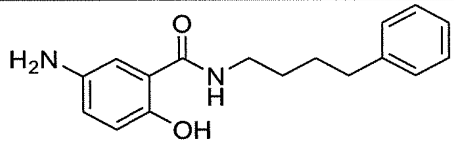
(b) cartridge was washed with 3 fractions of 4 mL of ethyl acetate the solvent was evaporated.

5

Table of compounds obtained by Method IV

ref n°	structure	Molec Wt.	HPLC	MS exp
40	 4-amino-*N*-(4-fluorobenzyl)-3-hydroxybenzamide	260	93	261.2
41	 4-amino-3-hydroxy-*N*-(2-naphthylmethyl)benzamide	292	81	293.1
42	 4-amino-3-hydroxy-*N*-(2-phenoxyethyl)benzamide	272	91	272
43	 4-amino-3-hydroxy-*N*-[1-(2-naphthyl)ethyl]benzamide	306	96	307.2
44	 4-amino-3-hydroxy-*N*-(2-	256	94	257.2

ref n°	structure	Molec Wt.	HPLC	MS exp
	phenylethyl)benzamide			
45	 4-amino-3-hydroxy-*N*-(3-phenylpropyl)benzamide	270	82	271.3
46	 4-amino-3-hydroxy-*N*-(4-phenylbutyl)benzamide	284	93	285.1
47	 5-amino-*N*-benzyl-2-hydroxybenzamide	242	98	243
48	 5-amino-2-hydroxy-*N*-(2-hydroxybenzyl)benzamide	258	98	257
49	 5-amino-*N*-(4-fluorobenzyl)-2-hydroxybenzamide	260	92	260
50		240	97	302

ref n°	structure	Molec Wt.	HPLC	MS exp
	5-amino-*N*-(3,5-dimethoxybenzyl)-2-hydroxybenzamide			
51	 5-amino-2-hydroxy-*N*-(2-naphthylmethyl)benzamide	292	93	284
52	 5-amino-2-hydroxy-*N*-(2-phenoxyethyl)benzamide	272	97	272
53	 5-amino-2-hydroxy-*N*-(2-phenylethyl)benzamide	256	97	256
54	 5-amino-2-hydroxy-*N*-(3-phenylpropyl)benzamide	270	98	270
55	 5-amino-2-hydroxy-*N*-(4-phenylbutyl)benzamide	284	92	284

The following compounds are prepared essentially according to the methods and procedures described above.

Name

N^1-hydroxy-N^2-[2-(4-methylphenyl)propanoyl]serinamide

N^1-hydroxy-N^2-[2-(4-methylphenyl)propanoyl]threoninamide

N^1-hydroxy-N^2-[2-(4-methylphenyl)propanoyl]cysteinamide

3-amino-N^1-hydroxy-N^2-[2-(4-methylphenyl)propanoyl]alaninamide

N-((hydroxycarbamoyl)methyl)-2-p-tolylpropanamide

N^2-(biphenyl-4-ylacetyl)-N^1-hydroxyserinamide

N^2-(biphenyl-4-ylacetyl)-N^1-hydroxyserinamide

N^2-(biphenyl-4-ylacetyl)-N^1-hydroxycysteinamide

3-amino-N^2-(biphenyl-4-ylacetyl)-N^1-hydroxyalaninamide

N^2-(biphenyl-4-ylacetyl)-N^1-hydroxyglycinamide

N-(1-(hydroxycarbamoyl)-2-hydroxyethyl)-1-p-tolylcyclopentanecarboxamide

N-(1-(hydroxycarbamoyl)-2-hydroxypropyl)-1-p-tolylcyclopentanecarboxamide

N-(1-(hydroxycarbamoyl)-2-mercaptoethyl)-1-p-tolylcyclopentanecarboxamide

N-(1-(hydroxycarbamoyl)-2-aminoethyl)-1-p-tolylcyclopentanecarboxamide

N-((hydroxycarbamoyl)methyl)-1-p-tolylcyclopentanecarboxamide

N^1-hydroxy-N^2-[3-(2-hydroxyphenyl)propanoyl]serinamide

N^1-hydroxy-N^2-[3-(2-hydroxyphenyl)propanoyl]threoninamide

N^1-hydroxy-N^2-[3-(2-hydroxyphenyl)propanoyl]cysteinamide

3-amino-N^1-hydroxy-N^2-[3-(2-hydroxyphenyl)propanoyl]alaninamide

N-((hydroxycarbamoyl)methyl)-3-(2-hydroxyphenyl)propanamide

N-(1-(hydroxycarbamoyl)-2-hydroxyethyl)-4-phenylbutanamide

N^1-hydroxy-N^2-(4-phenylbutanoyl)threoninamide

N-(1-(hydroxycarbamoyl)-2-mercaptoethyl)-4-phenylbutanamide

N-(1-(hydroxycarbamoyl)-2-aminoethyl)-4-phenylbutanamide

N-((hydroxycarbamoyl)methyl)-4-phenylbutanamide

N-(1-(hydroxycarbamoyl)-2-hydroxyethyl)-4-p-tolylbutanamide

N^1-hydroxy-N^2-[4-(4-methylphenyl)butanoyl]threoninamide

N-(1-(hydroxycarbamoyl)-2-mercaptoethyl)-4-p-tolylbutanamide

N-(1-(hydroxycarbamoyl)-2-aminoethyl)-4-p-tolylbutanamide

N-((hydroxycarbamoyl)methyl)-4-p-tolylbutanamide

(E)-N-(1-(hydroxycarbamoyl)-2-hydroxyethyl)-3-(furan-2-yl)acrylamide

2-((E)-3-(furan-3-yl)acrylamido)-N,3-dihydroxybutanamide

(E)-N-(1-(hydroxycarbamoyl)-2-mercaptoethyl)-3-(furan-2-yl)-2-methylacrylamide

3-amino-N^2-[(2*E*)-3-(2-furyl)prop-2-enoyl]-N^1-hydroxyalaninamide

(E)-N-((hydroxycarbamoyl)methyl)-3-(furan-2-yl)acrylamide

N-(1-(hydroxycarbamoyl)-2-hydroxyethyl)-1H-indole-3-carboxamide

N-(1-(hydroxycarbamoyl)-2-hydroxypropyl)-1H-indole-3-carboxamide

N-(1-(hydroxycarbamoyl)-2-mercaptoethyl)-1H-indole-3-carboxamide

N-(1-(hydroxycarbamoyl)-2-aminoethyl)-1H-indole-3-carboxamide

N-((hydroxycarbamoyl)methyl)-1H-indole-3-carboxamide

N-(1-(hydroxycarbamoyl)-2-hydroxyethyl)-1H-indole-2-carboxamide

N-(1-(hydroxycarbamoyl)-2-hydroxypropyl)-1H-indole-2-carboxamide

N-(1-(hydroxycarbamoyl)-2-hydroxyethyl)-1H-indole-2-carboxamide

N-(1-(hydroxycarbamoyl)-2-aminoethyl)-1H-indole-2-carboxamide

N-((hydroxycarbamoyl)methyl)-1H-indole-2-carboxamide

(E)-N-(1-(hydroxycarbamoyl)-2-hydroxyethyl)cinnamamide

2-(cinnamamido)-N,3-dihydroxybutanamide

(E)-N-(1-(hydroxycarbamoyl)-2-mercaptoethyl)cinnamamide

(E)-N-(1-(hydroxycarbamoyl)-2-aminoethyl)cinnamamide

(E)-N-((hydroxycarbamoyl)methyl)cinnamamide;

N^1-hydroxy-N^2-(2-hydroxy-3-nitrobenzyl)serinamide

N^1-hydroxy-N^2-(2-hydroxy-3-nitrobenzyl)threoninamide

N^1-hydroxy-N^2-(2-hydroxy-3-nitrobenzyl)cysteinamide

3-amino-N^1-hydroxy-N^2-(2-hydroxy-3-nitrobenzyl)alaninamide

N^1-hydroxy-N^2-(2-hydroxy-3-nitrobenzyl)glycinamide

N^1-hydroxy-N^2-[(4-methoxy-2-naphthyl)methyl]serinamide

N^1-hydroxy-N^2-[(4-methyl-2-naphthyl)methyl]threoninamide - methanol (1:1)

N^1-hydroxy-N^2-[(4-methoxy-2-naphthyl)methyl]cysteinamide

3-amino-N^1-hydroxy-N^2-[(4-methoxy-2-naphthyl)methyl]alaninamide

N^1-hydroxy-N^2-[(4-methoxy-2-naphthyl)methyl]glycinamide

N^1-hydroxy-N^2-(2-nitrobenzyl)serinamide

N^1-hydroxy-N^2-(2-nitrobenzyl)threoninamide

N^1-hydroxy-N^2-(2-nitrobenzyl)cysteinamide

3-amino-N^1-hydroxy-N^2-(2-nitrobenzyl)alaninamide

N^1-hydroxy-N^2-(2-nitrobenzyl)glycinamide

N^2-(biphenyl-2-ylmethyl)-N^1-hydroxyserinamide

N^2-(biphenyl-2-ylmethyl)-N^1-hydroxythreoninamide

N^2-(biphenyl-2-ylmethyl)-N^1-hydroxycysteinamide

3-amino-N^2-(biphenyl-2-ylmethyl)-N^1-hydroxyalaninamide

N^2-(biphenyl-2-ylmethyl)-N^1-hydroxyglycinamide

N^2-(2-fluoro-6-methoxybenzyl)-N^1-hydroxyserinamide

N^2-(2-fluoro-6-methoxybenzyl)-N^1-hydroxythreoninamide

N^2-(2-fluoro-6-methoxybenzyl)-N^1-hydroxycysteinamide

3-amino-N^2-(2-fluoro-6-methoxybenzyl)-N^1-hydroxyalaninamide

N^2-(2-fluoro-6-methoxybenzyl)-N^1-hydroxyglycinamide

N^1-hydroxy-N^2-(2-hydroxy-6-methoxybenzyl)serinamide

N^1-hydroxy-N^2-(2-hydroxy-6-methoxybenzyl)threoninamide

N^1-hydroxy-N^2-(2-hydroxy-6-methoxybenzyl)cysteinamide

3-amino-N^1-hydroxy-N^2-(2-hydroxy-6-methoxybenzyl)alaninamide

N^1-hydroxy-N^2-(2-hydroxy-6-methoxybenzyl)glycinamide

N^1-hydroxy-N^2-[(1-hydroxy-2-naphthyl)methyl]serinamide

N^1-hydroxy-N^2-[(1-hydroxy-2-naphthyl)methyl]threoninamide

N^1-hydroxy-N^2-[(1-hydroxy-2-naphthyl)methyl]cysteinamide

3-amino-N^1-hydroxy-N^2-[(1-hydroxy-2-naphthyl)methyl]alaninamide

N^1-hydroxy-N^2-[(1-hydroxy-2-naphthyl)methyl]glycinamide

N^2-[4-(benzyloxy)benzyl]-N^1-hydroxyserinamide

N^2-[4-(benzyloxy)benzyl]-N^1-hydroxythreoninamide

N^2-[4-(benzyloxy)benzyl]-N^1-hydroxycysteinamide

3-amino-N^2-[4-(benzyloxy)benzyl]-N^1-hydroxyalaninamide

N^2-[4-(benzyloxy)benzyl]-N^1-hydroxyglycinamide

N^2-(3-fluoro-4-methylbenzyl)-N^1-hydroxyserinamide

N^2-(3-fluoro-4-methylbenzyl)-N^1-hydroxythreoninamide

N^2-(3-fluoro-4-methylbenzyl)-N^1-hydroxycysteinamide

3-amino-N^2-(3-fluoro-4-methylbenzyl)-N^1-hydroxyalaninamide

N^2-(3-fluoro-4-methylbenzyl)-N^1-hydroxyglycinamide

N^1-hydroxy-N^2-(2-naphthylmethyl)serinamide

N^1-hydroxy-N^2-(2-naphthylmethyl)threoninamide

N^1-hydroxy-N^2-(2-naphthylmethyl)cysteinamide

3-amino-N^1-hydroxy-N^2-(2-naphthylmethyl)alaninamide

N^1-hydroxy-N^2-(2-naphthylmethyl)glycinamide;

N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxyserinamide

N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxythreoninamide

N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxycysteinamide

3-amino-N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxyalaninamide

N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxyglycinamide

N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]serinamide

N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]threoninamide

N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]cysteinamide

3-amino-N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]alaninamide

N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]glycinamide

N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxyserinamide

N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxythreoninamide

N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxycysteinamide

3-amino-N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxyalaninamide

N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxyglycinamide

N^1-hydroxy-N^2-(2-naphthylsulfonyl)serinamide

N^1-hydroxy-N^2-(2-naphthylsulfonyl)threoninamide

N^1-hydroxy-N^2-(2-naphthylsulfonyl)cysteinamide

3-amino-N^1-hydroxy-N^2-(2-naphthylsulfonyl)alaninamide

N^1-hydroxy-N^2-(2-naphthylsulfonyl)glycinamide

N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]serinamide

N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]threoninamide

N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]cysteinamide

3-amino-N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]alaninamide

N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]glycinamide

N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]serinamide

N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]threoninamide

N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]cysteinamide

$_3$-amino-N_1-hydroxy-N_2-[($_4$-methylphenyl)sulfonyl]alaninamide

N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]glycinamide

N^1-hydroxy-N^2-{[4-(trifluoromethyl)phenyl]sulfonyl}serinamide

N^1-hydroxy-N^2-{[4-(trifluoromethyl)phenyl]sulfonyl}serinamide

N^1-hydroxy-N^2-{[4-(trifluoromethyl)phenyl]sulfonyl}cysteinamide

3-amino-N^1-hydroxy-N^2-{[4-(trifluoromethyl)phenyl]sulfonyl}alaninamide

N^1-hydroxy-N^2-{[4-(trifluoromethyl)phenyl]sulfonyl}glycinamide

N^1-hydroxy-N^2-{[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}serinamide

N^1-hydroxy-N^2-{[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}threoninamide

N^1-hydroxy-N^2-{[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}cysteinamide

3-amino-N^1-hydroxy-N^2-{[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}alaninamide

N^1-hydroxy-N^2-{[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}glycinamide

N^1-hydroxy-N^2-(quinolin-7-ylsulfonyl)serinamide

N^1-hydroxy-N^2-(quinolin-7-ylsulfonyl)threoninamide

N^1-hydroxy-N^2-(quinolin-7-ylsulfonyl)cysteinamide

3-amino-N^1-hydroxy-N^2-(quinolin-7-ylsulfonyl)alaninamide

N^1-hydroxy-N^2-(quinolin-7-ylsulfonyl)glycinamide

N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxyserinamide

N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxythreoninamide

N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxycysteinamide

3-amino-N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxyalaninamide

N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxyglycinamide;

N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxyserinamide

N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxythreoninamide

N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxycysteinamide

3-amino-N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxyalaninamide

N^2-(biphenyl-4-ylsulfonyl)-N^1-hydroxyglycinamide

N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]serinamide

N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]threoninamide

N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]cysteinamide

3-amino-N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]alaninamide

N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]glycinamide

N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxyserinamide

N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxythreoninamide

N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxycysteinamide

3-amino-N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxyalaninamide

N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxyglycinamide

N^1-hydroxy-N^2-(2-naphthylsulfonyl)serinamide

N^1-hydroxy-N^2-(2-naphthylsulfonyl)threoninamide

N^1-hydroxy-N^2-(2-naphthylsulfonyl)cysteinamide

3-amino-N^1-hydroxy-N^2-(2-naphthylsulfonyl)alaninamide

N^1-hydroxy-N^2-(2-naphthylsulfonyl)glycinamide

N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]serinamide

N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]threoninamide

N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]cysteinamide

3-amino-N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]alaninamide

N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]glycinamide

N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]serinamide

N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]threoninamide

N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]cysteinamide

N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]glycinamide

N^1-hydroxy-N^2-{[4-(trifluoromethyl)phenyl]sulfonyl}serinamide

N^1-hydroxy-N^2-{[4-(trifluoromethyl)phenyl]sulfonyl}serinamide

N^1-hydroxy-N^2-{[4-(trifluoromethyl)phenyl]sulfonyl}cysteinamide

3-amino-N^1-hydroxy-N^2-{[4-(trifluoromethyl)phenyl]sulfonyl}alaninamide

N^1-hydroxy-N^2-{[4-(trifluoromethyl)phenyl]sulfonyl}glycinamide

N^1-hydroxy-N^2-{[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}serinamide

N^1-hydroxy-N^2-{[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}threoninamide

N^1-hydroxy-N^2-{[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}cysteinamide

3-amino-N^1-hydroxy-N^2-{[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}alaninamide

N^1-hydroxy-N^2-{[2-nitro-4-(trifluoromethyl)phenyl]sulfonyl}glycinamide

N^1-hydroxy-N^2-(quinolin-7-ylsulfonyl)serinamide

N^1-hydroxy-N^2-(quinolin-7-ylsulfonyl)threoninamide

N^1-hydroxy-N^2-(quinolin-7-ylsulfonyl)cysteinamide

3-amino-N^1-hydroxy-N^2-(quinolin-7-ylsulfonyl)alaninamide

N^1-hydroxy-N^2-(quinolin-7-ylsulfonyl)glycinamide

N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxyserinamide

N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxythreoninamide

N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxycysteinamide

3-amino-N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxyalaninamide

N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxyglycinamide;

N-hydroxy-*N*'-(2-hydroxy-5-methylphenyl)phthalamide

N-hydroxy-*N*'-(2-hydroxy-5-methylphenyl)biphenyl-2,2'-dicarboxamide

N-hydroxy-*N*'-(2-hydroxy-5-methylphenyl)naphthalene-1,8-dicarboxamide

N-hydroxy-*N*'-(2-hydroxy-5-methylphenyl)succinamide

N-hydroxy-*N*'-(2-hydroxy-4-nitrophenyl)phthalamide

N-hydroxy-*N*'-(2-hydroxy-4-nitrophenyl)biphenyl-2,2'-dicarboxamide

N-hydroxy-*N*'-(2-hydroxy-4-nitrophenyl)naphthalene-1,8-dicarboxamide

N-hydroxy-*N*'-(2-hydroxy-4-nitrophenyl)succinamide

N-hydroxy-*N*'-(2-hydroxy-3-methylphenyl)phthalamide

N-hydroxy-*N*'-(2-hydroxy-3-methylphenyl)biphenyl-2,2'-dicarboxamide

N-hydroxy-*N*'-(2-hydroxy-3-methylphenyl)naphthalene-1,8-dicarboxamide

N-hydroxy-*N*'-(2-hydroxy-3-methylphenyl)succinamide

N-hydroxy-*N*'-(2-hydroxyphenyl)phthalamide

N-hydroxy-*N*'-(2-hydroxyphenyl)biphenyl-2,2'-dicarboxamide

N-hydroxy-*N*'-(2-hydroxyphenyl)naphthalene-1,8-dicarboxamide

N-hydroxy-*N*'-(2-hydroxyphenyl)succinamide

N-hydroxy-*N*'-(3-hydroxy-2-naphthyl)phthalamide

N-hydroxy-*N*'-(3-hydroxy-2-naphthyl)biphenyl-2,2'-dicarboxamide

N-hydroxy-*N*'-(3-hydroxy-2-naphthyl)naphthalene-1,8-dicarboxamide

N-hydroxy-*N*'-(3-hydroxy-2-naphthyl)succinamide

N-hydroxy-*N*'-(2-mercaptophenyl)phthalamide

N-hydroxy-*N*'-(2-mercaptophenyl)biphenyl-2,2'-dicarboxamide

N-hydroxy-*N*'-(2-mercaptophenyl)naphthalene-1,8-dicarboxamide

N-hydroxy-*N*'-(2-mercaptophenyl)succinamide

N-(3-acetylphenyl)-*N*'-hydroxyphthalamide

N-(3-acetylphenyl)-*N*'-hydroxybiphenyl-2,2'-dicarboxamide

N-(3-acetylphenyl)-*N*'-hydroxynaphthalene-1,8-dicarboxamide

N-(3-acetylphenyl)-*N*'-hydroxysuccinamide

N-hydroxy-*N*'-(2-nitropyridin-3-yl)phthalamide

N-hydroxy-*N*'-(2-nitropyridin-3-yl)biphenyl-2,2'-dicarboxamide

N-hydroxy-*N*'-(2-nitropyridin-3-yl)naphthalene-1,8-dicarboxamide

N-hydroxy-*N*'-(2-nitropyridin-3-yl)succinamide

N-(2-aminophenyl)-*N*'-hydroxyphthalamide

N-(2-aminophenyl)-*N*'-hydroxybiphenyl-2,2'-dicarboxamide

N-(2-aminophenyl)-*N*'-hydroxynaphthalene-1,8-dicarboxamide

N-(2-aminophenyl)-*N*'-hydroxysuccinamide

N-(8-amino-1-naphthyl)-*N*'-hydroxyphthalamide

N-(8-amino-1-naphthyl)-*N*'-hydroxybiphenyl-2,2'-dicarboxamide

N-(8-amino-1-naphthyl)-*N*'-hydroxynaphthalene-1,8-dicarboxamide

N-(8-amino-1-naphthyl)-*N*'-hydroxysuccinamide;

2-[(2-hydroxy-4-methylbenzoyl)amino]isonicotinamide

N-[5-(aminocarbonyl)-2-hydroxyphenyl]-2-hydroxy-4-methylbenzamide

2-[(biphenyl-4-ylcarbonyl)amino]isonicotinamide

N-[5-(aminocarbonyl)-2-hydroxyphenyl]biphenyl-4-carboxamide

2-[(4-*tert*-butylbenzoyl)amino]isonicotinamide

3-[(4-*tert*-butylbenzoyl)amino]-4-hydroxybenzamide

2-[(1-hydroxy-2-naphthoyl)amino]isonicotinamide

N-[5-(aminocarbonyl)-2-hydroxyphenyl]-1-hydroxy-2-naphthamide

2-[(3-hydroxy-2-naphthoyl)amino]isonicotinamide

N-[5-(aminocarbonyl)-2-hydroxyphenyl]-3-hydroxy-2-naphthamide

N-[4-(aminocarbonyl)pyridin-2-yl]quinoline-6-carboxamide

N-[5-(aminocarbonyl)-2-hydroxyphenyl]quinoline-6-carboxamide

N-[4-(aminocarbonyl)pyridin-2-yl]isoquinoline-3-carboxamide

N-[5-(aminocarbonyl)-2-hydroxyphenyl]isoquinoline-3-carboxamide

N-[4-(aminocarbonyl)pyridin-2-yl]pyridine-2-carboxamide

N-[5-(aminocarbonyl)-2-hydroxyphenyl]pyridine-2-carboxamide

N-[4-(aminocarbonyl)pyridin-2-yl]-2-mercaptonicotinamide

N-[5-(aminocarbonyl)-2-hydroxyphenyl]-2-mercaptonicotinamide

N-[4-(aminocarbonyl)pyridin-2-yl]isoquinoline-1-carboxamide

N-[5-(aminocarbonyl)-2-hydroxyphenyl]isoquinoline-1-carboxamide;

2-({[(2-hydroxy-5-methylphenyl)amino]carbonyl}amino)isonicotinamide

4-hydroxy-3-({[(2-hydroxy-5-methylphenyl)amino]carbonyl}amino)benzamide

2-({[(2-hydroxy-4-nitrophenyl)amino]carbonyl}amino)isonicotinamide

4-hydroxy-3-({[(2-hydroxy-4-nitrophenyl)amino]carbonyl}amino)benzamide

2-({[(2-hydroxy-6-methylphenyl)amino]carbonyl}amino)isonicotinamide

4-hydroxy-3-({[(2-hydroxy-6-methylphenyl)amino]carbonyl}amino)benzamide

2-({[(2-hydroxyphenyl)amino]carbonyl}amino)isonicotinamide

4-hydroxy-3-({[(2-hydroxyphenyl)amino]carbonyl}amino)benzamide

2-({[(3-hydroxy-2-naphthyl)amino]carbonyl}amino)isonicotinamide

4-hydroxy-3-({[(3-hydroxy-2-naphthyl)amino]carbonyl}amino)benzamide

2-({[(2-mercaptophenyl)amino]carbonyl}amino)isonicotinamide

4-hydroxy-3-({[(2-mercaptophenyl)amino]carbonyl}amino)benzamide

2-({[(3-acetylphenyl)amino]carbonyl}amino)isonicotinamide

3-({[(3-acetylphenyl)amino]carbonyl}amino)-4-hydroxybenzamide

2-({[(2-nitropyridin-3-yl)amino]carbonyl}amino)isonicotinamide

4-hydroxy-3-({[(2-nitropyridin-3-yl)amino]carbonyl}amino)benzamide

2-({[(2-aminophenyl)amino]carbonyl}amino)isonicotinamide

3-({[(2-aminophenyl)amino]carbonyl}amino)-4-hydroxybenzamide

2-({[(8-amino-1-naphthyl)amino]carbonyl}amino)isonicotinamide

3-({[(8-amino-1-naphthyl)amino]carbonyl}amino)-4-hydroxybenzamide;

4-{[(biphenyl-4-ylsulfonyl)amino]methyl}-*N*-hydroxybenzamide

N-hydroxy-4-({[(4-propylphenyl)sulfonyl]amino}methyl)benzamide

4-[({[4-(1,1-dimethylpropyl)phenyl]sulfonyl}amino)methyl]-*N*-hydroxybenzamide

N-hydroxy-4-{[(2-naphthylsulfonyl)amino]methyl}benzamide

N-hydroxy-4-({[(4-methyl-3-nitrophenyl)sulfonyl]amino}methyl)benzamide

N-hydroxy-4-({[(4-methylphenyl)sulfonyl]amino}methyl)benzamide

N-hydroxy-4-[({[4-(trifluoromethyl)phenyl]sulfonyl}amino)methyl]benzamide

N-hydroxy-4-({[(4-methyl-2-nitrophenyl)sulfonyl]amino}methyl)benzamide

N-hydroxy-4-{[(quinolin-7-ylsulfonyl)amino]methyl}benzamide

4-[({[8-(dimethylamino)-2-naphthyl]sulfonyl}amino)methyl]-*N*-hydroxybenzamide

N-hydroxy-4-({[2-(4-methylphenyl)propanoyl]amino}methyl)benzamide

4-{[(biphenyl-4-ylacetyl)amino]methyl}-*N*-hydroxybenzamide

N-hydroxy-4-[({[1-(4-methylphenyl)cyclopentyl]carbonyl}amino)methyl]benzamide

N-hydroxy-4-({[3-(2-hydroxyphenyl)propanoyl]amino}methyl)benzamide

N-hydroxy-4-{[(4-phenylbutanoyl)amino]methyl}benzamide

N-hydroxy-4-({[4-(4-methylphenyl)butanoyl]amino}methyl)benzamide

4-({[(2*E*)-3-(2-furyl)prop-2-enoyl]amino}methyl)-*N*-hydroxybenzamide

N-{4-[(hydroxyamino)carbonyl]benzyl}-1*H*-indole-3-carboxamide

N-{4-[(hydroxyamino)carbonyl]benzyl}-1*H*-indole-2-carboxamide

N-hydroxy-4-({[(2*E*)-3-(4-methylphenyl)prop-2-enoyl]amino}methyl)benzamide

N-hydroxy-4-{[(2-hydroxy-3-nitrobenzyl)amino]methyl}benzamide

N-hydroxy-4-({[(4-methoxy-1-naphthyl)methyl]amino}methyl)benzamide

N-hydroxy-4-{[(2-nitrobenzyl)amino]methyl}benzamide

4-{[(biphenyl-2-ylmethyl)amino]methyl}-*N*-hydroxybenzamide

4-{[(2-fluoro-6-methoxybenzyl)amino]methyl}-*N*-hydroxybenzamide

N-hydroxy-4-{[(2-hydroxy-6-methoxybenzyl)amino]methyl}benzamide

N-hydroxy-4-({[(2-hydroxy-1-naphthyl)methyl]amino}methyl)benzamide

4-({[4-(benzyloxy)benzyl]amino}methyl)-*N*-hydroxybenzamide

4-{[(3-fluoro-4-methylbenzyl)amino]methyl}-*N*-hydroxybenzamide

N-hydroxy-4-{[(2-naphthylmethyl)amino]methyl}benzamide

N-hydroxy-4-[({[(2-hydroxy-6-methylphenyl)amino]carbonyl}amino)methyl]benzamide

N-hydroxy-4-[({[(2-hydroxy-4-nitrophenyl)amino]carbonyl}amino)methyl]benzamide

N-hydroxy-4-[({[(2-hydroxyphenyl)amino]carbonyl}amino)methyl]benzamide

N-hydroxy-4-[({[(3-hydroxy-2-naphthyl)amino]carbonyl}amino)methyl]benzamide

N-hydroxy-4-[({[(2-mercaptophenyl)amino]carbonyl}amino)methyl]benzamide

4-[({[(3-acetylphenyl)amino]carbonyl}amino)methyl]-*N*-hydroxybenzamide

N-hydroxy-4-[({[(2-nitropyridin-3-yl)amino]carbonyl}amino)methyl]benzamide

4-[({[(2-aminophenyl)amino]carbonyl}amino)methyl]-*N*-hydroxybenzamide

4-[({[(8-amino-1-naphthyl)amino]carbonyl}amino)methyl]-*N*-hydroxybenzamide;

methyl N^5-hydroxy-N^2-[2-(4-methylphenyl)propanoyl]glutaminate

ethyl N^5-hydroxy-N^2-[2-(4-methylphenyl)propanoyl]glutaminate

methyl N^2-(biphenyl-4-ylacetyl)-N^5-hydroxyglutaminate

ethyl N^2-(biphenyl-4-ylacetyl)-N^5-hydroxyglutaminate

methyl N^5-hydroxy-N^2-{[1-(4-methylphenyl)cyclopentyl]carbonyl}glutaminate

ethyl N^5-hydroxy-N^2-{[1-(4-methylphenyl)cyclopentyl]carbonyl}glutaminate

methyl N^5-hydroxy-N^2-[3-(2-hydroxyphenyl)propanoyl]glutaminate

ethyl N^5-hydroxy-N^2-[3-(2-hydroxyphenyl)propanoyl]glutaminate

methyl N^5-hydroxy-N^2-(4-phenylbutanoyl)glutaminate

ethyl N^5-hydroxy-N^2-(4-phenylbutanoyl)glutaminate

methyl N^5-hydroxy-N^2-[4-(4-methylphenyl)butanoyl]glutaminate

ethyl N^5-hydroxy-N^2-[4-(4-methylphenyl)butanoyl]glutaminate

methyl N^2-[(2*E*)-3-(3-furyl)prop-2-enoyl]-N^5-hydroxyglutaminate

ethyl N^2-[(2*E*)-3-(2-furyl)prop-2-enoyl]-N^5-hydroxyglutaminate

methyl N^5-hydroxy-N^2-(1*H*-indol-3-ylcarbonyl)glutaminate

ethyl N^5-hydroxy-N^2-(1*H*-indol-3-ylcarbonyl)glutaminate

methyl N^5-hydroxy-N^2-(1*H*-indol-2-ylcarbonyl)glutaminate

ethyl N^5-hydroxy-N^2-(1*H*-indol-2-ylcarbonyl)glutaminate

methyl N^5-hydroxy-N^2-[(2*E*)-3-(4-methylphenyl)prop-2-enoyl]glutaminate

ethyl N^5-hydroxy-N^2-[(2*E*)-3-(4-methylphenyl)prop-2-enoyl]glutaminate

1-(2-hydroxy-4-methylbenzoyl)prolinamide

N-hydroxy-1-(2-hydroxy-4-methylbenzoyl)prolinamide

1-(biphenyl-4-ylcarbonyl)prolinamide

1-(biphenyl-4-ylcarbonyl)-*N*-hydroxyprolinamide

1-(4-*tert*-butylbenzoyl)prolinamide

1-(4-*tert*-butylbenzoyl)-*N*-hydroxyprolinamide

1-(1-hydroxy-2-naphthoyl)prolinamide

N-hydroxy-1-(1-hydroxy-2-naphthoyl)prolinamide

1-(3-hydroxy-2-naphthoyl)prolinamide

N-hydroxy-1-(3-hydroxy-2-naphthoyl)prolinamide

1-(quinolin-6-ylcarbonyl)prolinamide

N-hydroxy-1-[(7-hydroxyquinolin-6-yl)carbonyl]prolinamide

1-(isoquinolin-3-ylcarbonyl)prolinamide

N-hydroxy-1-(isoquinolin-3-ylcarbonyl)prolinamide

1-(pyridin-2-ylcarbonyl)prolinamide

N-hydroxy-1-(pyridin-2-ylcarbonyl)prolinamide

1-[(2-mercaptopyridin-3-yl)carbonyl]prolinamide

N-hydroxy-1-[(2-mercaptopyridin-3-yl)carbonyl]prolinamide

1-(isoquinolin-1-ylcarbonyl)prolinamide

N-hydroxy-1-(isoquinolin-1-ylcarbonyl)prolinamide;

4-amino-*N*-benzyl-3-hydroxybenzamide

4-amino-3-hydroxy-*N*-(2-hydroxybenzyl)benzamide

4-amino-*N*-(4-fluorobenzyl)-3-hydroxybenzamide

4-amino-*N*-(3,5-dimethoxybenzyl)-3-hydroxybenzamide

4-amino-3-hydroxy-*N*-(2-naphthylmethyl)benzamide

4-amino-3-hydroxy-*N*-(2-phenoxyethyl)benzamide

4-amino-3-hydroxy-*N*-[1-(2-naphthyl)ethyl]benzamide

4-amino-3-hydroxy-*N*-(2-phenylethyl)benzamide

4-amino-3-hydroxy-*N*-(3-phenylpropyl)benzamide

4-amino-3-hydroxy-*N*-(4-phenylbutyl)benzamide;

5-amino-*N*-benzyl-2-hydroxybenzamide

5-amino-2-hydroxy-*N*-(2-hydroxybenzyl)benzamide

5-amino-*N*-(4-fluorobenzyl)-2-hydroxybenzamide

5-amino-*N*-(3,5-dimethoxybenzyl)-2-hydroxybenzamide

5-amino-2-hydroxy-*N*-(2-naphthylmethyl)benzamide

5-amino-2-hydroxy-*N*-(2-phenoxyethyl)benzamide

5-amino-2-hydroxy-*N*-[1-(2-naphthyl)ethyl]benzamide

5-amino-2-hydroxy-*N*-(2-phenylethyl)benzamide

5-amino-2-hydroxy-*N*-(3-phenylpropyl)benzamide and

5-amino-2-hydroxy-*N*-(4-phenylbutyl)benzamide.

The above names were generated using ChemDraw Ultra v. 9.0.1, which is available from CambridgeSoft.

Example 4

SSAO activity determination: All assays were performed at 37°C with SSAO from human or mice adipose tissue. The enzyme activity was measured through detection of hydrogen peroxide formed by the oxidation of benzylamine. This method is based on the horseradish peroxidase catalyzed hydrogen peroxide oxidation of 10-acetyl-3, 7-dihydroxyphenoxazine (Molecular Probes A-6550), that produces resorufin a highly fluorescent product (excitation, 545 nm; emission, 590 nm) (Zhou and Panchuk-Voloshina, 1997). Human or mice adipose tissue homogenates, used as a source of SSAO activity, were preincubated in 96 well microplates for 20 min at 37°C in 180 µL of 200 mM Phosphate buffer and H_2O_2-detecting mixture containing horseradish peroxidase (final concentration 1 U/mL) and Amplex Red reagent (60 µM) and different concentrations of inhibitors when necessary. Catalytic reaction was initiated by addition of 20 µL of benzylamine as substrate at 10 mM for human homogenates giving final concentrations of 100 µM and 1 mM respectively. Fluorescence intensity of the samples was measured continuously during 1 h (excitation, 545 nm; emission,

590 nm) and H_2O_2 concentration was calculated from calibration curves generated by serial dilutions of standard H_2O_2. To evaluate the amount of H_2O_2 formed specifically via SSAO-mediated reaction, semicarbazide 100 μM was included in the control wells subjected to the same treatments and these values were subtracted from the total amount of H_2O_2 formed.

The inhibition was measured as % decrease of the signal compared to a control without inhibitor. Blank values in absence of substrates were subtracted from the fluorescence for each experimental condition. The IC_{50} shown in Table 1 were calculated with GraphPad Prism 4 program.

Table I

Ref. N°	IC_{50}, μM on Human SSAO
1	0.39 ± 0.07
2	1.10 ± 0.04
3	0.10 ± 0.03
4	0.033 ± 0.006
5	0.25 ± 0.02
6	0.3 ± 0.1
7	1.9 ± 0.2
8	0.066 ± 0.001
9	0.136 ± 0.040
10	0.041 ± 0.008
11	0.0040 ± 0.0005
12	1.575 ± 0.175
13	0.067 ± 0.001
14	0.054 ± 0.007
15	0.217 ± 0.039
16	0.028 ± 0.008
17	0.217 ± 0.039
18	0.041 ± 0.001
19	0.140 ± 0.030
20	0.789 ± 0.061
21	0.097 ± 0.021

Ref. N°	IC_{50}, μM on Human SSAO
22	0.369 ± 0.071
23	0.70 ± 0.04
24	0.334 ± 0.080
25	0.941 ± 0.026
26	0.125 ± 0.002
27	0.214 ± 0.041
28	0.229 ± 0.092
29	0.259 ± 0.062
30	0.165 ± 0.007
31	0.128 ± 0.03
32	0.121 ± 0.047
33	0.090 ± 0.002
34	0.147 ± 0.044
35	0.160 ± 0.031
36	0.078 ± 0.024
37	0.18 ± 0.01
38	0.14 ± 0.01
39	0.39 ± 0.04
40	0.202 ± 0.026
41	0.25 ± 0.056
42	0.173 ± 0.009
43	0.337 ± 0.07
44	0.185 ± 0.031
45	0.146 ± 0.005
46	0.401 ± 0.030
47	0.41 ± 0.063
48	0.074
49	0.253 ± 0.002
50	0.577 ± 0.027
51	0.477± 0.064
52	0.189 ± 0.016

Ref. N°	IC_{50}, μM on Human SSAO
53	0.618 ± 0.118
54	0.575 ± 0.023
55	0.762 ± 0.060

It should be understood that the foregoing disclosure emphasizes certain specific embodiments of the invention and that all modifications or alternatives equivalent thereto are within the spirit and scope of the invention as set forth in the appended claims.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the invention and that modifications may be made therein without departing from the spirit or scope of the invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

What is claimed is:

1. A compound of formula:

$$R_3\text{-}(Y)_n\text{-}(CR_2R_2)_m\text{-}Z$$

or a pharmaceutically acceptable salt thereof, wherein

m is 0 or 1-6;

n is 0 or 1-6;

Z is $CONR_1OH$, COOH, $B(OH)_2$, SO_2NR_1OH, OR_1, SR_1, NHR_1, PO_3H, CH_2NHR_1, COR_1, $CONHR_1$, $CHNR_1$, or CNR_1NHR_1;

Y is –CO-, -CS-, $-NR_2OR_2$-, $-NR_2$-, $-SR_2$-, $-NR_2SO_2R_2$-, $-COR_2$-, $-NR_2$-$C(NR_2)$-NR_2-, –(C_1-C_6 alkyl)-NHC(O)-, –(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, -NHC(O)-, -N(C_1-C_6alkyl)C(O)-, -C(O)NH-, -C(O)-N(C_1-C_6alkyl), $-SO_2NH$-, $-SO_2$-N(C_1-C_6alkyl)-, -(C_1-C_6 alkyl)-C(O)NH-, –(C_1-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, -O–(C_1-C_6 alkyl)-NHC(O)-, or -O–(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH or =O;

R_1 at each occurrence is independently H, C_1-C_6 alkyl, aryl, substituted aryl, heterocycloalkyl containing at least one and no more than two heteroatoms selected from S, N, and O, or C_3-C_7 cycloalkyl, and where any member of the alkyl, aryl/or cycloalkyl group is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, aryl or substituted aryl;

R_2 at each occurrence is independently H, C_1-C_6 alkyl, aryl, substituted aryl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, C_3-C_7 cycloalkylalkoxy, heteroaryl, heteroarylalkyl, heterocycloalkyl, or heterocycloalkylalkyl, where each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, amide, amine, C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl or nitrile; and

R_3 is aryl, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkyl C_1-C_6 alkyl, C_3-C_7 cycloalkyl C_1-C_6 alkoxy, heteroaryl, heterocycloalkyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, haloalkyl, haloalkoxy, nitro, CN, CO_2H, C_1-C_6 alkylthio, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_6 acyloxy, aryl, heteroaryl, or hydroxyl;

2. A compound according to claim 1, wherein

Z is $CONR_1OH$, COOH, NHR_1, CH_2NHR_1, $CONHR_1$, or $CHNR_1$; wherein

R_1 at each occurrence is independently H, or C_1-C_6 alkyl, phenyl, naphthyl, binaphthyl, piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, S,S-dioxomorpholinyl, or C_3-C_7 cycloalkyl, where each of the above is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, phenyl, or naphthyl, wherein the phenyl and naphthyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, amide, amine, C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl or nitrile.

3. A compound according to claim 1, wherein

Y is –CO-, $-COR_2$-, –(C_1-C_6 alkyl)-NHC(O)-, –(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, -NHC(O)-, -N(C_1-C_6alkyl)C(O)-, -C(O)NH-, -C(O)-N(C_1-C_6alkyl), $-SO_2NH$-, $-SO_2$-N(C_1-C_6alkyl)-, -(C_1-C_6 alkyl)-C(O)NH-, –(C_1-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, -O–(C_1-C_6 alkyl)-NHC(O)-, or -O–(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH or =O, wherein

R_2 at each occurrence is independently H, C_1-C_6 alkyl, phenyl, naphthyl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, C_3-C_7 cycloalkylalkoxy, pyridyl, thienyl, furanyl, imidazolyl, pyrimidyl, pyrrolyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, S,S-dioxomorpholinyl, piperidinyl C_1-C_4 alkyl, piperazinyl C_1-C_4 alkyl, pyrrolidinyl C_1-C_4 alkyl, morpholinyl C_1-C_4 alkyl, S,S-dioxomorpholinyl C_1-C_4 alkyl, where each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, amide, amine, C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl or nitrile.

4. A compound according to claim 1, wherein

R_3 is aryl, selected from phenyl, naphthyl, indanyl, and biphenyl, C_5-C_6 cycloalkyl, C_5-C_6 cycloalkyl C_1-C_6 alkyl, C_5-C_6 cycloalkyl C_1-C_6 alkoxy, heteroaryl, selected from

pyridyl, pyrimidyl, indolyl, pyrrolyl, thienyl, furanyl, thiazolyl, pyrazolyl, and oxazolyl, heterocycloalkyl, selected from piperazinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, and S,S-dioxothiomorpholinyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, nitro, CN, CO_2H, C_1-C_6 alkylthio, C_1-C_6 acyloxy, phenyl, pyridyl, thienyl, furanyl, pyrimidyl, or hydroxy.

5. A compound according to claim 1, wherein

n is 1-4;

m is 1-4;

Z is $CONR_1OH$, COOH, NHR_1, CH_2NHR_1, $CONHR_1$, or $CHNR_1$; wherein

R_1 at each occurrence is independently H, or C_1-C_6 alkyl, phenyl, naphthyl, binaphthyl, piperidinyl, pyrrolidinyl, piperazinyl, morpholinyl, S,S-dioxomorpholinyl, or C_3-C_7 cycloalkyl, where each of the above is optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, phenyl, or naphthyl, wherein the phenyl and naphthyl groups are optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, halogen, nitro, carboxylic acid, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl or nitrile;

Y is –CO-, $-COR_2$-, –(C_1-C_6 alkyl)-NHC(O)-, –(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, -NHC(O)-, -N(C_1-C_6alkyl)C(O)-, -C(O)NH-, -C(O)-N(C_1-C_6alkyl), $-SO_2NH$-, $-SO_2$-N(C_1-C_6alkyl)-, -(C_1-C_6 alkyl)-C(O)NH-, –(C_1-C_6 alkyl)-C(O)-N(C_1-C_6alkyl)-, -O–(C_1-C_6 alkyl)-NHC(O)-, or -O–(C_1-C_6 alkyl)-N(C_1-C_6 alkyl)C(O)-, wherein the alkyl portion or portions of each of the above is optionally substituted with 1, 2, or 3 groups that are independently halogen, C_1-C_4 alkoxy, amino, mono or di (C_1-C_6 alkyl)amino, OH or =O; wherein

R_2 at each occurrence is independently H, C_1-C_6 alkyl, phenyl, naphthyl, C_1-C_6 alkoxy, C_1-C_6 alkoxyalkyl, C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylalkyl, C_3-C_7 cycloalkylalkoxy, pyridyl, thienyl, furanyl, imidazolyl, pyrimidyl, pyrrolyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, S,S-dioxomorpholinyl, piperidinyl C_1-C_4 alkyl, piperazinyl C_1-C_4 alkyl, pyrrolidinyl C_1-C_4 alkyl, morpholinyl C_1-C_4 alkyl, S,S-dioxomorpholinyl C_1-C_4 alkyl, where each of the above is optionally substituted with 1, 2, 3, 4, or 5 groups that are

independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, aryl, substituted aryl, halogen, nitro, nitroso, aldehyde, carboxylic acid, amide, amine, C_1-C_6 alkoxycarbonyl, sulfate, imine, hydroxyl or nitrile; and

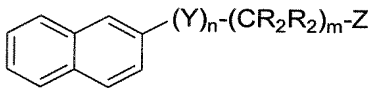
R_3 is aryl selected from phenyl, naphthyl, indanyl, and biphenyl, C_5-C_6 cycloalkyl, heteroaryl selected from pyridyl, pyrimidyl, indolyl, pyrrolyl, thienyl, furanyl, thiazolyl, pyrazolyl, and oxazolyl, heterocycloalkyl selected from piperazinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, and S,S-dioxothiomorpholinyl, each of which is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, CF_3, OCF_3, nitro, CN, CO_2H, C_1-C_6 alkylthio, C_1-C_6 acyloxy, phenyl, pyridyl, thienyl, furanyl, pyrimidyl, or hydroxy.

6. A compound according to claim 5, wherein

Z is $CONR_1OH$, or NHR_1, wherein

R_1 at each occurrence is independently H, or C_1-C_6 alkyl, wherein the alkyl group is optionally substituted with halogen, or C_1-C_6 alkoxy, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, halogen, nitro, carboxylic acid, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl.

7. A compound according to claim 6, of the formula



8. A compound according to claim 7, wherein

Z is $CONR_1OH$, and

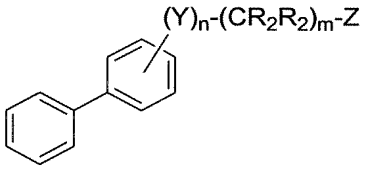
R_1 is independently H, or C_1-C_6 alkyl, wherein the alkyl group is optionally substituted with halogen, or C_1-C_6 alkoxy, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, halogen, nitro, carboxylic acid, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl.

9. A compound according to claim 8, wherein n is 1 and m is 1, 2, or 3.

10. A compound according to claim 9, wherein Z is $CONR_1OH$, and R_1 is H.

11. A compound according to claim 9, wherein Z is $CONR_1OH$, and R_1 is C_1-C_4 alkyl.

12. A compound according to claim 6, of the formula:



13. A compound according to claim 12, wherein Z is $CONR_1OH$, and

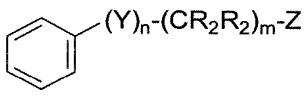
R_1 is independently H, or C_1-C_6 alkyl, wherein the alkyl group is optionally substituted with halogen, or C_1-C_6 alkoxy, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, halogen, nitro, carboxylic acid, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl.

14. A compound according to claim 13, wherein n is 1 and m is 1, 2,or 3.

15. A compound according to claim 14, wherein Z is $CONR_1OH$, and R_1 is H.

16. A compound according to claim 14, wherein Z is $CONR_1OH$, and R_1 is C_1-C_4 alkyl.

17. A compound according to claim 6, of the formula:



18. A compound according to claim 17, wherein Z is $CONR_1OH$, and

R_1 is independently H, or C_1-C_6 alkyl, wherein the alkyl group is optionally substituted with halogen, or C_1-C_6 alkoxy, or phenyl, wherein the phenyl group is optionally substituted with 1, 2, 3, 4, or 5 groups that are

independently halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, halogen, nitro, carboxylic acid, $C(O)NH_2$, $C(O)NH(C_1$-C_6 alkyl), $C(O)N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_6 alkyl), hydroxyl.

19. A compound according to claim 18, wherein n is 1 and m is 1, 2, or 3.

20. A compound according to claim 19, wherein Z is $CONR_1OH$, and R_1 is H.

21. A compound according to claim 19, wherein Z is $CONR_1OH$, and R_1 is C_1-C_4 alkyl.

22. A compound according to any one of claims 1-20, wherein the compound inhibits a copper-containing amine oxidase.

23. A compound according to claim 22, wherein the compound inhibits semicarbazide-sensitive amine oxidase.

24 A compound according to claim 1 that is:

N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-*N*^{1}-hydroxythreoninamide;

N^1-hydroxy-*N*^{2}-[(4-methyl-3-nitrophenyl)sulfonyl]serinamide;

N^1-hydroxy-*N*^{2}-[(2-methyl-1*H*-indol-3-yl)acetyl]glycinamide;

N^1-hydroxy-*N*^{2}-[(4-methylphenyl)sulfonyl]threoninamide;

N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-*N*^{1}-hydroxyserinamide;

N^1-hydroxy-*N*^{2}-(2-naphthylsulfonyl)threoninamide;

N^1-hydroxy-*N*^{2}-[(4-propylphenyl)sulfonyl]serinamide;

N^1-hydroxy-*N*^{2}-(2-naphthylsulfonyl)serinamide;

5-amino-2-hydroxy-*N*-(2-hydroxybenzyl)benzamide;

1-(isoquinolin-1-ylcarbonyl)prolinamide;

N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-*N*^{1}-hydroxyserinamide;

N^1-hydroxy-*N*^{2}-[(4-bromophenyl)carbonyl]glycinamide;

1-(biphenyl-4-ylcarbonyl)prolinamide;

N-(biphenyl-4-ylacetyl)glutamic acid;

N-[(2*E*)-3-(4-methylphenyl)prop-2-enoyl]glutamic acid;

N^1-hydroxy-*N*^{2}-[(4-propylphenyl)sulfonyl]threoninamide;

N-hydroxy-*N*'-(2-hydroxyphenyl)succinamide;

3-amino-N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]alaninamide;
4-amino-3-hydroxy-*N*-(3-phenylpropyl)benzamide;
1-(3-hydroxy-2-naphthoyl)prolinamide;
1-(quinolin-6-ylcarbonyl)prolinamide;
N-(1*H*-indol-2-ylcarbonyl)glutamic acid;
4-amino-3-hydroxy-*N*-(2-phenoxyethyl)benzamide;
N-hydroxy-*N'*-(1-methyl-3-phenylpropyl)succinamide;
4-amino-3-hydroxy-*N*-(2-phenylethyl)benzamide;
5-amino-2-hydroxy-*N*-(2-phenoxyethyl)benzamide;
or a pharmaceutically-acceptable salt thereof.

25. A method of treating an animal having a disease or disorder characterized by pathological expression of a copper-containing amine oxidase enzyme, comprising administering to an animal in need of such treatment an inhibitor of said copper-containing amine oxidase at a therapeutically-active concentration, wherein the activity of the enzyme is inhibited thereby.

26. A method according to claim 25, wherein the copper-containing amine oxidase is semicarbazide-sensitive amine oxidase.

27. A method according to claim 25, wherein the animal is a human.

28. A method according to claim 25, wherein the disease or disorder is an inflammatory disease, an adipocyte dysfunction related disease, a carbohydrate metabolism related disease, a vascular disease, a neurodegenerative disease or cancer.

29. A method according to claim 28, wherein said inflammatory disease is rheumatoid arthritis, osteoarthritis, spondylitis, bone resorption disease, sepsis, septic shock, chronic pulmonary inflammatory disease, fever, periodontal diseases, ulcerative colitis, pyresis, cystic fibrosis, dysfunctions of the immune system, multiple sclerosis, inflammatory eye conditions including uveitis, glaucoma or conjunctivitis.

30. A method according to claim 28, wherein said inflammatory disease is degenerative bone or joint conditions including osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis,

gouty arthritis ankylosing spondylitis, psoriatic arthritis and other arthritic conditions, or joint inflammation.

31. A method according to claim 28, wherein said inflammatory disease is a chronic inflammatory skin condition, that is allergic lesions, lichen planus, pityriasis rosea, eczema, psoriasis, or dermatitis.

32. A method according to claim 28, wherein said inflammatory disease is a disease or disorder of the gastrointestinal tract, that is inflammatory bowel disease, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, peptic ulceration, particularly irritable bowel syndrome, reflux oesophagitis, and damage to the gastrointestinal tract resulting from infections by *Helicobacter pylori* or other infectious organism or from treatments with non-steroidal anti-inflammatory drugs;

33. A method according to claim 28, wherein said inflammatory disease is an inflammatory lung disorder that is asthma, bronchitis, particularly chronic obstructive pulmonary disease, farmer's lung, or acute respiratory distress syndrome.

34. A method according to claim 28, wherein said inflammatory disease is meningitis, pancreatitis, bacteraemia, endotoxaemia (septic shock), aphthous ulcers, gingivitis, pyresis, or pain, comprising inflammatory pain, neuropathic pain, acute pain or pain of a central origin.

35. A method according to claim 28, wherein said inflammatory disease is a central nervous system inflammatory condition or disease comprising multiple sclerosis, Alzheimer's disease, or ischaemia-reperfusion injury associated with ischemic stroke.

36. A method according to claim claim 28, wherein the carbohydrate metabolism related disease is diabetes or a complication of diabetes that is a microvascular or macrovascular disease comprising atherosclerosis, vascular retinopathies, nephropathies, neuropathies, joint problems or foot ulcers.

37. A method according to claim 28, wherein the adipocyte metabolism dysfunction is obesity or complications thereof comprising diabetes, hypertension or atherosclerosis.

38. A method according to claim 28, wherein the neurodegenerative disease is Alzheime's disease or Parkinson's disease.

39. A method according to claim 28, wherein the vascular disease is atheromatous and nonatheromatous arteriosclerosis, ischemic heart disease, or Raynaud's Disease and Phenomenon.

40. A method according to claim 25, wherein the disease or disorder is atherosclerosis, a neurodegenerative disease, obesity, hypertension or cancer.

41. A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically-acceptable salt thereof and a pharmaceutically-acceptable excipient, diluent or adjuvant thereof.

42. A pharmaceutical composition according to claim 31, wherein the compound is:
N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxythreoninamide;
N^1-hydroxy-N^2-[(4-methyl-3-nitrophenyl)sulfonyl]serinamide;
N^1-hydroxy-N^2-[(2-methyl-1*H*-indol-3-yl)acetyl]glycinamide;
N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]threoninamide;
N^2-{[4-(1,1-dimethylpropyl)phenyl]sulfonyl}-N^1-hydroxyserinamide;
N^1-hydroxy-N^2-(2-naphthylsulfonyl)threoninamide;
N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]serinamide;
N^1-hydroxy-N^2-(2-naphthylsulfonyl)serinamide;
5-amino-2-hydroxy-*N*-(2-hydroxybenzyl)benzamide;
1-(isoquinolin-1-ylcarbonyl)prolinamide;
N^2-{[8-(dimethylamino)-2-naphthyl]sulfonyl}-N^1-hydroxyserinamide;
N^1-hydroxy-N^2-[(4-bromophenyl)carbonyl]glycinamide;
1-(biphenyl-4-ylcarbonyl)prolinamide;
N-(biphenyl-4-ylacetyl)glutamic acid;
N-[(2*E*)-3-(4-methylphenyl)prop-2-enoyl]glutamic acid;
N^1-hydroxy-N^2-[(4-propylphenyl)sulfonyl]threoninamide;
N-hydroxy-*N'*-(2-hydroxyphenyl)succinamide;
3-amino-N^1-hydroxy-N^2-[(4-methylphenyl)sulfonyl]alaninamide;
4-amino-3-hydroxy-*N*-(3-phenylpropyl)benzamide;

1-(3-hydroxy-2-naphthoyl)prolinamide;

1-(quinolin-6-ylcarbonyl)prolinamide;

N-(1*H*-indol-2-ylcarbonyl)glutamic acid;

4-amino-3-hydroxy-*N*-(2-phenoxyethyl)benzamide;

N-hydroxy-*N*'-(1-methyl-3-phenylpropyl)succinamide;

4-amino-3-hydroxy-*N*-(2-phenylethyl)benzamide;

5-amino-2-hydroxy-*N*-(2-phenoxyethyl)benzamide;

or a pharmaceutically-acceptable salt thereof.

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUNDS FOR INHIBITING COPPER-CONTAINING AMINE OXIDASES AND USES THEREOF

(57) Abstract: This invention is directed to inhibitors of copper-containing amine oxidases (E.C.1.4.3.6) including semicarbazide-sensitive amine oxidase (SSAO; also known as vascular adhesion protein- 1, VAP-I), and their therapeutic use in inflammatory diseases, diabetes and its associated complications, atherosclerosis, neurodegenerative diseases, obesity, hypertension and cancer.

WO 2006/013209 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/053778

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/165 A61K31/166 A61K31/167 A61K31/18 A61K31/198
A61K31/401 A61K31/404 A61K31/47 A61K31/4709 C07C259/00
A61K31/16 A61K31/405

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07D C07C A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, MEDLINE, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"The merck index twelfth edition" 1996, MERCK RESEARCH LABORATORIES , U.S.A , XP002372930 page 12, paragraph 60.	1,2
X	page 183, paragraph 1122	1-4
X	page 1247, paragraph 7390	1-4
X	MERCK: "Reagenzien : Chemikalien . Diagnostika" 1996, MERCK , DARMSTADT GERMANY , XP002372931 page 275, paragraph 820130	1-4

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2006	21/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kling, I

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/053778

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1988, MORPURGO L ET AL: "SPECTROSCOPIC STUDIES OF THE REACTION BETWEEN BOVINE SERUM AMINE OXIDASE COPPER-CONTAINING AND SOME HYDRAZIDES AND HYDRAZINES" XP002372934 Database accession no. PREV198987046960 abstract & BIOCHEMICAL JOURNAL, vol. 256, no. 2, 1988, pages 565-570, ISSN: 0264-6021	1-4
X	US 2004/122011 A1 (MASFERRER JAIME L ET AL) 24 June 2004 (2004-06-24) page 58; tables 6,9	1-4
X	WO 99/32150 A (WARNER-LAMBERT COMPANY; PETERSON, JOSEPH, THOMAS, JR; PRESSLER, MILTON) 1 July 1999 (1999-07-01) page 1 pages 127-128	1-4
X	EP 1 331 224 A (SHIONOGI & CO., LTD) 30 July 2003 (2003-07-30) abstract	1-6
X	WO 98/26773 A (WARNER-LAMBERT COMPANY; BOCAN, THOMAS, MICHAEL, ANDREW; BOXER, PETER,) 25 June 1998 (1998-06-25) claims 6-11	1-4
E	WO 2005/082343 A (LA JOLLA PHARMACEUTICAL COMPANY; SALTER-CID, LUISA, MARIA; WANG, ERIC,) 9 September 2005 (2005-09-09) claims 1-49	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/053778

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 25-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims 1-4 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1 -4

The search of claims 1-4 was restricted to the different variables possibles for the different R, Y, Z and n and m.

The subject-matter of claim 25 and the dependents claims 26 to 41 is even braoder than the scope of the claims 1 -23.

The search of claims 25 -41 was restricted to the inhibitors of cooper-containing amine oxidase and in particular to the inhibitors of cooper-containing amine oxidase which are semicarbazide-sensitive amine oxidase.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/053778

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